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Lactams. XIII.[1] Alkylation of Lactim Ethers: A Novel Synthetic Route to N-(2-Arylethyl)lactams from N-Unsubstituted Lactams[2]

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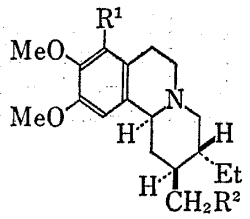
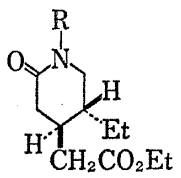
Treatment of the lactim ethers (**10a—d, 11a—c**), prepared from N-unsubstituted 5-, 6-, and 7-membered lactams (**6a—d**), with phenacyl bromide or 3,4-dimethoxyphenacyl bromide in N,N-dimethylformamide at 60° for 1—6 hr furnished the corresponding N-substituted lactams (**21a—d, 22a—c**) in good yields. Conversion of the lactam ketones (**21a—d, 22a—c**) into the N-(2-arylethyl)lactams (**25a—d, 26a—c**) through the lactam alcohols (**23a—d, 24a—c**) was effected in excellent overall yields by $NaBH_4$ reduction followed by catalytic hydrogenolysis. In contrast, the alkylations of O-methylvalerolactim (**10b**) or O-ethylvalerolactim (**11b**) with less reactive alkyl halides (relative to phenacyl bromide) such as MeI, EtI, $PhCH_2Br$, $PhCH_2CH_2Br$, and $3,4\text{-}(MeO)_2C_6H_3CH_2CH_2Br$ were found to give mixtures of the normally N-alkylated 2-piperidones and N-methyl- or N-ethyl-2-piperidone presumed to have formed by the O→N methyl or ethyl migration during the reactions. Alkylations of the δ-valerolactam anion with 2-arylethyl bromide or its equivalents could afford the corresponding N-substituted 2-piperidones, but in unacceptable yields.

Keywords——lactam; lactim ether; N-alkylation; alkyl halide; $NaBH_4$ reduction; catalytic hydrogenolysis; O→N alkyl migration

In our previous and recent alkaloid syntheses in the *dl*-emetine (type **1**),[4] *dl*-ankorine (**2**),[4c] *dl*-alangicine (type **3**),[5] *dl*-alangimarckine (type **3**),[6] and related areas,[7] the synthetic strategy we adopted necessitated the operation of introducing an adequate phenethyl carbon skeleton onto the nitrogen of ethyl *dl-trans*-5-ethyl-2-oxo-4-piperidineacetate (**4**), which was



1 : R^1=H; R^2=a heterocyclic moiety
2 : R^1=OH; R^2=CH_2OH
3 : R^1=OH; R^2=a heterocyclic moiety



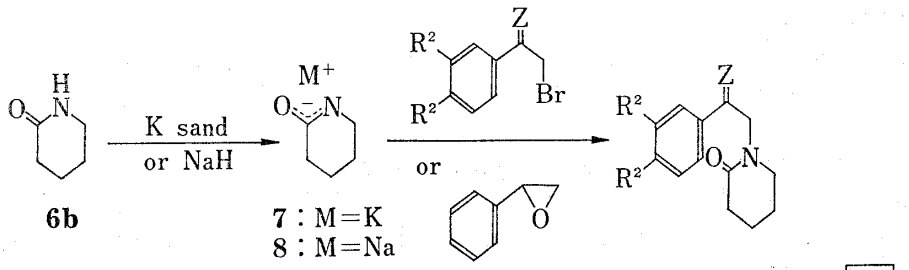
4 : R=H
5 : R=ArCH_2CH_2

Chart 1

1) Paper XII in this series, T. Fujii, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.* (Tokyo), **26**, 645 (1978).
2) A portion of this work was reported in a preliminary form by T. Fujii, S. Yoshifuji, and K. Yamada, *Chem. Ind.* (London), **1975**, 177.
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
4) *a*) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958); *b*) T. Fujii and S. Yoshifuji, Abstracts of Papers, 40th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, June 21, 1975, p. 3; *c*) T. Fujii, S. Yoshifuji, and K. Yamada, *Tetrahedron Lett.*, **1975**, 1527.
5) T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, *Tetrahedron Lett.*, **1976**, 2553.
6) T. Fujii, S. Yoshifuji, and H. Kogen, *Tetrahedron Lett.*, **1977**, 3477.
7) T. Fujii, S. Yoshifuji, and H. Ito, *Heterocycles*, **7**, 149 (1977).

readily prepared[1,4a] and characterized fully[8] in our laboratory. Such an operation to form the N-(2-arylethyl)lactam derivative (type **5**) would be feasible by the reaction of 2-arylethyl bromide with the potassium or sodium salt of **4**. A few precedents,[4a,9-11] however, indicated that this type of alkylation required drastic reaction conditions and yield of the desired N-(2-aryl)ethylated product was usually low owing to the competitive elimination reaction of the starting bromide to form the corresponding styrene derivative.[11] Thus, prior to the above alkaloid syntheses,[4b,c,5-7] we were compelled to carry out some model experiments in order to find out an alternative method. This paper reports the results of our pursuit along this line, which opened a new, general synthetic route to N-(2-arylethyl)lactams (type **25** or **26**) from 5-, 6-, and 7-membered lactams (type **6**) through conversion into lactim ethers (type **10** or **11**) followed by N-alkylation with a phenacyl bromide, reduction of the phenacylcarbonyl group, and hydrogenolytic removal of the resulting benzylic hydroxyl group.

The first model selected for investigation was the reaction of the potassium salt (**7**) or the sodium salt (**8**) of 2-piperidone (**6b**) with 2-arylethyl bromide or its equivalents. Treatment of **7**, generated *in situ* from **6b** and potassium sand, with phenethyl bromide in boiling toluene for 22 hr in the presence of a little copper powder gave 1-phenethyl-2-piperidone (**25b**) but in 10% yield with the recovery of 41% of the starting lactam (**6b**). The presence of styrene in the reaction mixture was detected by gas-liquid chromatography (GLC). When the reaction of the sodium salt (**8**), generated *in situ* from **6b** and sodium hydride, with 3,4-dimethoxy-



6b

7 : M=K
8 : M=Na

9 : R^2=MeO; Z=O,O

22b : R^2=MeO; Z=O
23b : R^2=H; Z=H,OH
25b : R^2=H; Z=H_2
26b : R^2=MeO; Z=H_2

Chart 2

phenethyl bromide was effected in N,N-dimethylacetamide (20°, 12 hr) or hexamethylphosphoramide (3—4°, 5 hr), the yield of the desired product (**26b**) was similarly poor (11—13%). These results were in general agreement with those of the precedents[4a,9-11] described above, suggesting that the strongly basic lactam anion (as in **7** or **8**) had caused the 2-arylethyl bromides to undergo the *E*2 reaction competitively.

Thus, the phenethylating agent was then switched over to an equivalent that bore no β-hydrogens or should not suffer any elimination reaction. Condensation of **8** with 3,4-dimethoxyphenacyl bromide in N,N-dimethylformamide (DMF) or benzene at room temperature or at 50° provided a complicated reaction mixture, from which **22b** was isolated in only

8) T. Fujii, S. Yoshifuji, and M. Tai, *Chem. Pharm. Bull.* (Tokyo), **23**, 2094 (1975), and references cited.
9) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *Chem. Pharm. Bull.* (Tokyo), **21**, 2695 (1973).
10) S. Sugasawa and M. Kirisawa, *Pharm. Bull.* (Japan), **3**, 187 (1955).
11) *a*) S. Sugasawa, K. Sakurai, and N. Sugimoto, *Proc. Japan Acad.* (Tokyo), **15**, 82 (1939); *b*) *Idem*, *Yakugaku Zasshi*, **59**, 247 (1939).

13—22% yield. This sample was identical with the one obtained by the potassium permanganate oxidation of the lactam alcohol (**24b**). In the above condensation, replacement of the reactive bromide by 2-(3,4-dimethoxyphenyl)-2,2-ethylenedioxyethyl bromide, obtained by the ketalization[12] of 3,4-dimethoxyphenacyl bromide, failed to give the corresponding N-substituted lactam (**9**) under various reaction conditions. The failure is probably due to the steric bulk[13] of the ketalized bromide at the benzylic position. In an attempt to modify the procedure reported by Ziegenbein and Franke,[14] the sodium salt (**8**) was allowed to react with styrene oxide in benzene (refluxing, 6 hr) or DMF (100°, 6 hr). However, the yield of the lactam alcohol (**23b**) was again found to be unacceptable (8—17%).

Having been unsatisfied with the above results, we next tried to extend the scope of the N-alkylation[15] of O-methyl- (**10b**) and O-ethylvalerolactim (**11b**), which were less basic than the valerolactam anion (as in **7** or **8**) and were readily available equivalents[16] of **6b**. On treatment with one molar equivalent of methyl iodide at 60° for 6 hr, the O-methyllactim (**10b**) afforded the N-methyllactam (**15**) in 93% yield. A similar alkylation of **10b** with ethyl iodide, benzyl bromide, phenethyl bromide, or 3,4-dimethoxyphenethyl bromide produced the N-alkylated lactam (**12**, **13**, **25b**, or **26b**) as well as the N-methylated lactam (**15**).

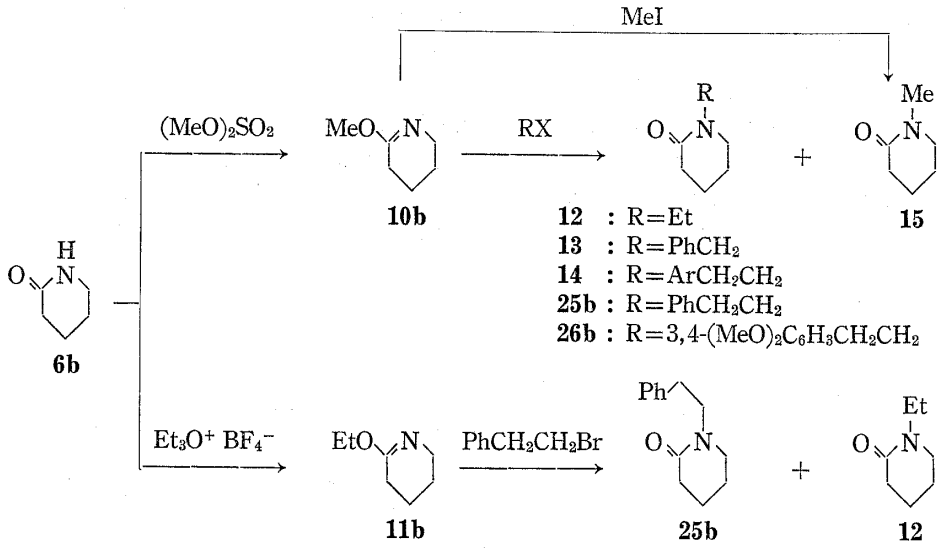


Chart 3

Likewise, a mixture of the N-phenethyllactam (**25b**) and the N-ethylated lactam (**12**) was obtained from the reaction of the O-ethyllactim (**11b**) with phenethyl bromide. It may be seen from Table I that an alkyl halide, whose alkyl group was different from that of the O-alkyl group of the lactim ether, reacted with the lactim ether to give both the normally N-alkylated and the O→N alkyl migration product. The use of an excess of the alkyl halide caused the extent of formation of the isomerized product to decrease. It is also noteworthy that an alkyl halide, less reactive than that whose alkyl group was the same as in the O-alkyllactim, gave a reaction mixture in which the isomerized product was predominant over the normally N-alkylated product. In the reaction with a more reactive alkyl halide, however, the normal N-alkylation was favored over the O→N alkyl migration. Comparison of the data on the phenethylation of **10b** and **11b** reveals that the use of the O-ethyllactim (**11b**)

12) The procedure followed that[24] of Kühn.
13) R. E. Flannery and K. G. Hampton, *J. Org. Chem.*, 37, 2806 (1972).
14) W. Ziegenbein and W. Franke, *Chem. Ber.*, **90**, 2291 (1957).
15) For a review, see R. G. Glushkov and V. G. Granik, "Advances in Heterocyclic Chemistry," Vol. 12, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1970, pp. 185—212.
16) *a*) J. W. Ralls, *J. Org. Chem.*, **26**, 66 (1961); *b*) T. Oishi, M. Nagai, T. Onuma, H. Moriyama, K. Tsutae, M. Ochiai, and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **17**, 2306 (1969).

Table I. Alkylation of Valerolactim Ethers (**10b**, **11b**) with Alkyl Halides (Chart 3)

Lactim ether	Alkyl halide RX	Reaction conditions[a] Amt. (molar eq)	Temp. (°C)	Time (hr)	Product N-Alkylated lactam	Yield (%)	Isomerized product	Yield (%)
10b	MeI	1	60	6	**15**	93	—	—
10b	EtI	1	60	48	**12**	18[b]	**15**	65[b]
10b	EtI	10	60	240	**12**	52[b]	**15**	34[b]
10b	$PhCH_2Br$	1	60	13	**13**	59	**15**	17
10b	$PhCH_2Br$	3	60	10	**13**	80	**15**	2
10b	$PhCH_2CH_2Br$	0.9	100	28	**25b**	7	**15**	50
10b	$3,4\text{-}(MeO)_2C_6H_3CH_2CH_2Br$	1	90	24	**26b**	8	**15**	—[c]
11b	$PhCH_2CH_2Br$	1	100	48	**25b**	27	**12**	12

a) All the reactions were carried out in tightly stoppered vessels or sealed tubes.
b) Determined by NMR spectroscopic analysis of both products isolated as a mixture.
c) No attempt was made to isolate the isomerized product (**15**), but its formation was detected by TLC of the reaction mixture.

rather than the O-methyllactim (**10b**) should be preferred as a method of the normal N-alkylation.

The above observations can be interpreted in terms of the mechanism[17] proposed for the transformation of O-methylcaprolactim (**10c**) into N-methylcaprolactam in the presence of dimethyl sulfate. As shown in Chart 4, the normally alkylated quaternary salt (**17**), produced by the reaction of **16** with an alkyl halide (R^4X), would undergo nucleophilic attack of the halide ion on the α-carbon of the alkoxyl group (R^3O) to yield the normally N-alkyl-

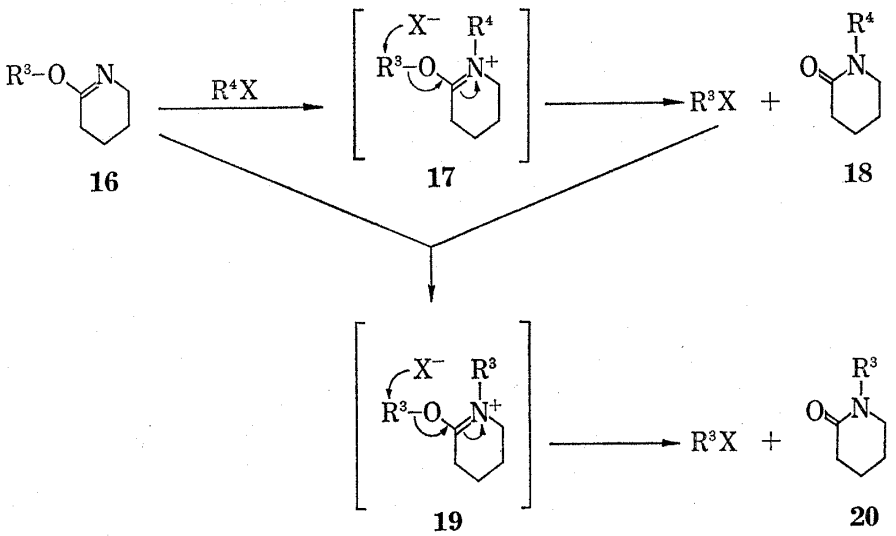


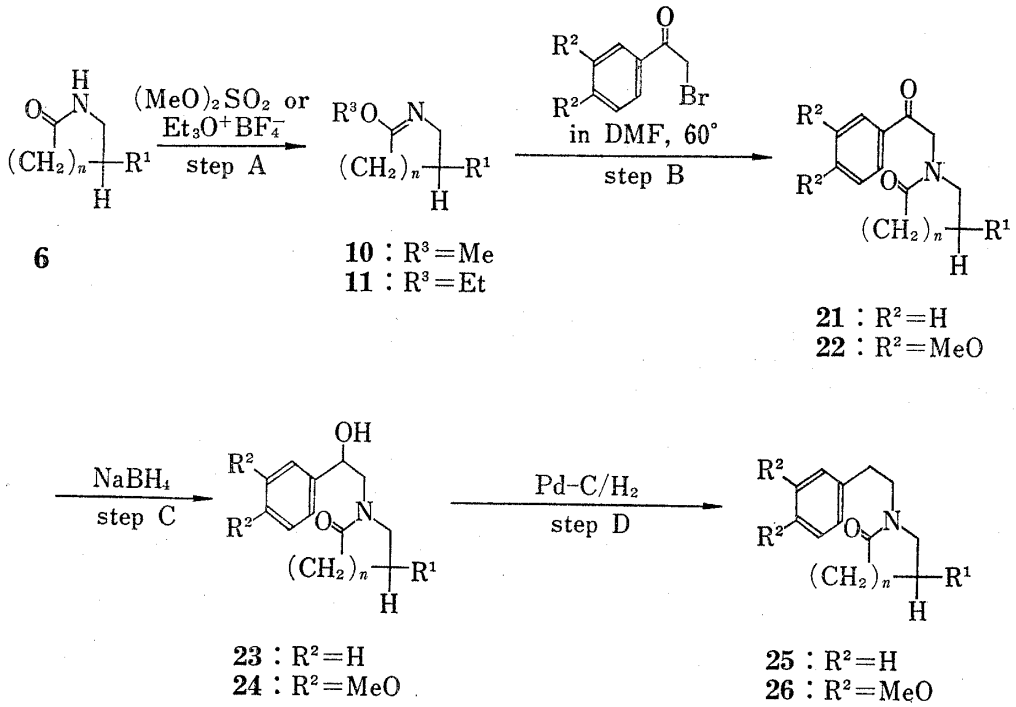
Chart 4

ated lactam (**18**) and R^3X. The alkyl halide (R^3X) thus generated could alkylate, competitively with R^4X, the unaltered **16** to give the quaternary salt (**19**), which would decompose to the isomerized product (**20**) and R^3X in a similar manner. Recycle of R^3X in such a way could finally transform all the remaining **16** into **20**.

Although the results in Table I indicated that the yields of the N-(2-arylethyl)-2-piperidones (type **14**) (**25b**, **26b**) were too low to bring the reactions with the alkyl halides of a

17) *a*) R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, **70**, 2115 (1948); *b*) J. W. Ralls and C. A. Ellinger, *Chem. Ind.* (London), **1961**, 20.

phenethyl-type into practice, they suggested that replacement of the less reactive bromide by a more reactive equivalent such as phenacyl bromide in this reaction would be promising. This suggestion proved to be pertinent when treatment of **10b** or **11b** with phenacyl bromide in DMF or without DMF at 60° for 1—4 hr was found to furnish N-phenacyl-2-piperidone (**21b**) in 91—94% yield (step B in Chart 5). A similar reaction with 3,4-dimethoxyphenacyl



6

10 : R^3=Me
11 : R^3=Et

21 : R^2=H
22 : R^2=MeO

23 : R^2=H
24 : R^2=MeO

25 : R^2=H
26 : R^2=MeO

a series : R^1=H; n=1
b series : R^1=H; n=2
c series : R^1=H; n=3
d series : R^1=Et; n=2

Chart 5

bromide (60°, 5—6 hr) produced N-(3,4-dimethoxyphenacyl)-2-piperidone (**22b**) in 88—92% yield. We further extended the scope of this new reaction to include other O-methyl- (**10a, c,d**) and O-ethyllactims (**11a,c**), which were prepared from the corresponding 5-, 6-, and 7-membered lactams (**6a,c,d**) according to previously reported procedures[18] in acceptable yields. Table II summarizes the results.

The next problem for solution was to transform the phenacyl moiety of the lactams into the phenethyl moiety, and it was settled as shown in Chart 5. Reduction of the lactam ketones (**21a—d, 22a—c**) with sodium borohydride (EtOH, room temp., 1—3 hr) gave the lactam alcohols (**23a—d, 24a—c**) in excellent yields (step C). Catalytic hydrogenolysis of the lactam alcohols (**23a—d, 24a—c**) in ethanol containing a small amount of perchloric acid (10% Pd-C/H_2, 3—4 atm, room temp., 1.5—4 hr)[9,19] afforded the expected N-(2-arylethyl)lactams (**25a—d, 26a—c**) in good yields (step D). The results are summarized in Table II. The

18) *a*) For **10a**, see S. Peterson and E. Tietze, *Chem. Ber.*, **90**, 909 (1957); *b*) For **11a**, see Z. Horii, K. Morikawa, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **17**, 2230 (1969); *c*) For **10b**, see ref. 16*a*; *d*) For **11b**, see ref. 16*b*; *e*) For **10c**, see R. E. Benson and T. L. Cairns, "Organic Syntheses," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 588.

19) *a*) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **20**, 1451 (1972); *b*) T. Fujii, K. Yoshida, M. Ohba, and S. Yoshifuji, *ibid.*, **25**, 2336 (1977); *c*) T. Fujii, M. Ohba, and S. Yoshifuji, *ibid.*, **25**, 3042 (1977).

Table II. Conversion of Lactim Ethers into N-(2-Arylethyl)lactams (Chart 5)

Compound series	Step B					Step C		Step D	
	Lactim ether	Reagent[a]	Reaction time (hr)	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
a	**10a**	PB	1	**21a**	93	**23a**	98	25a	98
a	**11a**	PB	2	**21a**	94				
a	**10a**	DPB	2	**22a**	87	**24a**	99	**26a**	92
b	**10b**	PB	3 (1)[b]	**21b**	91 (94)[b]	**23b**	98	**25b**	97
b	**11b**	PB	4	**21b**	94				
b	**10b**	DPB	5 (6)[b]	**22b**	88 (90)[b]	**24b**	98	**26b**	94
b	**11b**	DPB	5	**22b**	92				
c	**10c**	PB	6[b]	**21c**	92	**23c**	98	**25c**	94
c	**11c**	PB	5[b]	**21c**	98				
c	**10c**	DPB	6	**22c**	95	**24c**	99	**26c**	91
d	**10d**	PB	5	**21d**	91	**23d**[c]	97	**25d**	93

a) The abbreviation PB stands for phenacyl bromide; DPB, 3,4-dimethoxyphenacyl bromide.
b) Data on the reaction effected without solvent DMF.
c) As a diastereoisomeric mixture.

addition of perchloric acid in the last step for easier hydrogenolysis was based on our previous finding,[19a] and this procedure has been successfully applied to analogous lactam alcohols.[7,9,19b,c]

In conclusion, steps A, B, C, and D depicted in Chart 5 have provided a new synthetic route to N-(2-arylethyl)lactams from N-unsubstituted 5-, 6-, and 7-membered lactams. Although the route consists of four main steps, it will probably prove of general utility for introducing the phenethyl carbon skeleton onto the nitrogen of lactams carrying a variety of substituents because of the efficient chemical transformation and mild reaction conditions at each step. Our recent syntheses[4b,c,5–8,20] of some of the Ipecac and the *Alangium* alkaloids or related compounds from the common key intermediate (**4**) or an analogous derivative[20] have strongly exemplified its general synthetic utility.

Experimental

All melting points are corrected; boiling points, uncorrected. Spectra reported herein were measured with a JASCO-IRA-2 IR spectrophotometer, a JEOL-JMS-01SG mass spectrometer, or a JEOL-JNM-PS-100 NMR spectrometer at 23° using tetramethylsilane as an internal standard. For gas-liquid chromatography (GLC) a Shimadzu GC-3AH gas chromatograph, equipped with a 3 m×3 mm column containing 1.5% SE-30 (methyl silicone) on Chromosorb W, was used. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, m=multiplet, q=quartet, s=singlet, t=triplet.

Reaction of the Potassium Salt (7) or the Sodium Salt (8) of 2-Piperidinone (6b) with 2-Arylethyl Bromide or Its Equivalents (Chart 2)——i) With Phenethyl Bromide: To a stirred suspension of K sand (405 mg, 0.0104 g.-atom) in abs. toluene (5 ml) was added dropwise a solution of 2-piperidinone (**6b**) (991 mg, 10 mmol) in abs. toluene (15 ml), and the mixture was heated at reflux for 30 min. After cooling, a solution of phenethyl bromide (2.04 g, 11 mmol) in abs. toluene (15 ml) was added dropwise over a period of 15 min. The resulting mixture was refluxed for 22 hr with stirring in the presence of powdered Cu (0.1 g). After cooling, the Cu and KBr that precipitated were removed by filtration, and the filtrate was washed with H_2O and dried over anhyd. Na_2SO_4. The presence of styrene in the dried solution was detected by GLC analysis. The remaining toluene solution was then evaporated to dryness *in vacuo*, leaving a brown oil. The oil was chromatographed on an alumina column using $CHCl_3$ or $CHCl_3$–benzene (1: 1, v/v) as eluent. Fractions containing 1-phenethyl-2-piperidinone (**25b**) were combined and the solvent was removed by evaporation. The resulting, pale brownish solid was vacuum distilled to give **25b** (209 mg, 10%), bp 158—163° (bath temp.) (3 mmHg); mp 36—38°; IR $\nu_{max}^{CHCl_3}$ 1640 cm^{-1} (lactam CO). This sample was identical [by thin-layer chromatography (TLC) and infrared (IR) spectrum] with an authentic sample.[21] The aqueous washings described above were salted

20) T. Fujii, S. Yoshifuji, and K. Ikeda, *Heterocycles*, **5**, 183 (1976).
21) S. Akaboshi, T. Kutsuma, and K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **8**, 14 (1960).

out with anhyd. K_2CO_3 and the mixture was extracted with $CHCl_3$. From the dried $CHCl_3$ extracts was recovered 41% (404 mg) of the starting lactam (**6b**).

ii) With 3,4-Dimethoxyphenethyl Bromide: A mixture of **6b** (99 mg, 1 mmol) and NaH, which has been obtained from a 50% oil dispersion (55 mg) by washing with dry benzene, in hexamethylphosphoramide (HMPA) (5 ml) was heated at 70° for 1.5 hr. After cooling, 3,4-dimethoxyphenethyl bromide (294 mg, 1.2 mmol) was added under ice-cooling. The resulting mixture was stirred at 3—4° for 5 hr. After addition of H_2O (10 ml), the mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with 5% aq. HCl and H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave a pale brownish oil (245 mg). Purification of the oil by column chromatography [alumina, AcOEt–hexane (1: 1, v/v)] gave 1-(3,4-dimethoxyphenethyl)-2-piperidinone (**26b**) (33 mg, 13%) as a colorless solid, mp 48—52°, identical (by TLC and IR spectrum) with an authentic sample.[19a] A similar reaction of **8** in N,N-dimethylacetamide (DMAC) (20°, 12 hr) instead of HMPA afforded **26b** in 11% yield.

iii) With 3,4-Dimethoxyphenacyl Bromide: A mixture of **6b** (99 mg, 1 mmol) and NaH, obtained from a 50% oil dispersion (55 mg) by washing with abs. benzene, in abs. benzene (6 ml) was heated at 50° for 2 hr. After cooling, 3,4-dimethoxyphenacyl bromide[22] (310 mg, 1.2 mmol) was added under ice-cooling. The resulting, dark brownish turbid mixture was stirred at 25° for 2 hr then at 50° for 1.5 hr. After addition of H_2O (6 ml), the reaction mixture was extracted with benzene. The benzene extracts were washed successively with H_2O, 5% aq. HCl, and H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave a dark orange oil (405 mg). The oil was chromatographed on a 40-g alumina column using AcOEt–hexane (1: 1, v/v) as eluent, furnishing crude 1-(3,4-dimethoxyphenacyl)-2-piperidinone (**22b**) (76 mg). Recrystallization from AcOEt–hexane yielded colorless plates (61 mg, 22%), mp 89—90°, identical (by TLC, IR spectrum, and mixed melting-point test) with a sample of **22b** prepared by the $KMnO_4$ oxidation of **24b** (see below). When the above condensation was carried out in N,N-dimethylformamide (DMF) (8 ml) at 24° for 2 hr, the yield of **22b** was 13%.

iv) With 2-(3,4-Dimethoxyphenyl)-2,2-ethylenedioxyethyl Bromide: The sodium salt (**8**) of **6b** was generated *in situ* in a manner similar to that described above under item-(ii) and allowed to react with 2-(3,4-dimethoxyphenyl)-2,2-ethylenedioxyethyl bromide (1.2 molar eq) (for preparation, see below) in benzene (reflux, 6 hr), xylene (reflux, 10 hr), DMF (140°, 8 hr), DMAC (70°, 8 hr), HMPA (70°, 3 hr), or Me_2SO (room temp., 3 hr, or 90°, 6 hr). However, the desired compound (**9**) could not be obtained in any cases.

v) With Styrene Oxide: The sodium salt (**8**), generated *in situ* from **6b** (198 mg, 2 mmol) and a 50% oil dispersion (110 mg) of NaH in benzene (8 ml) (60°, 2.5 hr), was allowed to react with styrene oxide (360 mg, 3 mmol) in the same solvent at reflux for 6 hr. After cooling, 5% aq. HCl (5 ml) and H_2O (5 ml) were added and the resulting mixture was extracted with benzene. Drying of the extracts and evaporation of the solvent left a brown oil (390 mg), which was chromatographed on a 25-g alumina column using AcOEt–hexane as eluent. Fractions containing **23b** were combined and the solvent was removed by evaporation, leaving a colorless solid (35 mg, 8%), mp 107—108°, identical (by TLC and IR spectrum) with authentic 1-(2-hydroxy-2-phenylethyl)-2-piperidinone (**23b**).[23] A similar reaction of **8** in DMF (100°, 6 hr) furnished **23b** in 17% yield.

2-(3,4-Dimethoxyphenyl)-2,2-ethylenedioxyethyl Bromide——The following procedure was based on that reported[24] for the ketalization of phenacyl bromide. A mixture of 3,4-dimethoxyphenacyl bromide[22] (7.77 g, 30 mmol), ethylene glycol (2.23 g, 36 mmol), benzene (50 ml), and conc. H_2SO_4 (3 drops) was heated at reflux under a Dean-Stark water separator until one molar eq of H_2O had been removed (8.5 hr). After cooling, the reaction mixture was poured into a sat. solution of $NaHCO_3$ in H_2O with stirring. The benzene layer was separated from the aqueous layer, washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave a colorless solid (9.10 g, 100%), mp 68—71°. Recrystallization from MeOH produced the ketal as colorless prisms, mp 74—75°; NMR ($CDCl_3$) δ: 3.67 (2H, s, CH_2Br), 3.96 (6H, s, two MeO's), 3.72—4.28 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 6.85 (1H, d, J=8 Hz, $H_{(5')}$), 7.00—7.16 (2H, m, $H_{(2')}$ and $H_{(6')}$). *Anal.* Calcd. for $C_{12}H_{15}BrO_4$: C, 47.54; H, 4.99. Found: C, 47.38; H, 4.84.

Preparation of the Lactim Ethers (10a—d, 11a—c) (step A in Chart 5)——The lactim ethers (**10a—d**, (**11a—c**) were prepared from the corresponding lactams (**6a—d**) according to published procedures and characterized as follows. O-Methylbutyrolactim (**10a**),[18a] a colorless oil (42% yield), bp 35° (30 mmHg) (lit.[18a] bp 118—121°); IR ν_{max}^{film} 1654 cm^{-1} (C=N). O-Methylvalerolactim (**10b**),[16a] a colorless oil (70% yield), bp 52° (30 mmHg) [lit.[16a] bp 56° (32 mmHg)]; IR ν_{max}^{film} 1678 cm^{-1} (C=N). O-Methylcaprolactim (**10c**),[18e] a colorless oil (82% yield), bp 61° (19 mmHg) [lit.[18e] bp 65—67° (24 mmHg)]; IR ν_{max}^{film} 1677 cm^{-1} (C=N). 3-Ethyl-6-methoxy-2,3,4,5-tetrahydropyridine (**10d**), synthesized in 55% yield from 5-ethyl-2-piperidone (**6d**)[9] in a manner similar to that [16a] employed for **10b**, a colorless oil, bp 102° (55 mmHg); MS *m/e*: 141 (M^+); IR ν_{max}^{film} 1685 cm^{-1} (C=N); NMR ($CDCl_3$) δ: 0.85—1.04 (3H, unresolved t, $CH_2\underline{Me}$), 3.65 (3H, s, MeO). O-Ethylbutyrolactim (**11a**),[16b] a colorless oil (71% yield), bp 65—67° (51 mmHg) [lit.[18b] bp 50—60° (15

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23) H. Möhrle, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **297**, 474 (1964).
24) M. Kühn, *J. Prakt. Chem.* [2], **156**, 103 (1940).

mmHg)]; IR ν_{max}^{film} 1650 cm^{-1} (C=N); NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 1.77—2.24 (2H, m, $C\underline{H_2}CH_2N$), 2.31—2.61 (2H, m, $CH_2C{=}N$), 3.57—3.82 (2H, m, $C{=}NCH_2$), 4.19 (2H, q, J=7 Hz, $OC\underline{H_2}Me$). O-Ethylvalerolactim (**11b**),[16b] a colorless oil (84% yield), bp 87° (64 mmHg) [lit.[16b] 86—88° (70 mmHg)]; IR ν_{max}^{film} 1680 cm^{-1} (C=N). O-Ethylcaprolactim (**11c**), prepared in 82% yield from **6c** by application of the procedure[16b] adopted for **11b**, a colorless oil, bp 82° (28 mmHg) [lit.[18e] bp 81—82° (26 mmHg)]; IR ν_{max}^{film} 1677 cm^{-1} (C=N); NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.97 (2H, q, J=7 Hz, $OC\underline{H_2}Me$).

Reactions of O-Methylvalerolactim (10b) and O-Ethylvalerolactim (11b) with Alkyl Halide (Chart 3 and Table I)——The reactions of **10b** with methyl iodide, ethyl iodide, benzyl bromide, phenethyl bromide, and 3,4-dimethoxyphenethyl bromide and the reaction of **11b** with phenethyl bromide were effected under reaction conditions specified in Table I. To each of the reaction mixtures was added a sat. solution of K_2CO_3 in H_2O and the resulting mixtures were separately extracted with benzene or $CHCl_3$. The extracts were dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo*. The residual oils were then chromatographed on alumina or silica gel columns using hexane–acetone or hexane–AcOEt as eluent for isolation of the products. In the case of the reaction of **10b** with methyl iodide, the crude product was directly purified by vacuum distillation. In the case of the reaction of **10b** with ethyl iodide, the crude product mixture was also distilled *in vacuo* (17 mmHg). Since the TLC of the oily distillate indicated that it consisted of the N-methyl- (**15**) and N-ethyl-2-piperidinone (**12**), the nuclear magnetic resonance (NMR) spectrum of the mixture was measured in $CDCl_3$ and the areas of the N–Me and the C–Me signal were determined. The product ratio was then estimated from a calibration curve which had been constructed on analytical samples of **15** and **12**. The results of these alkylations are summarized in Table I and the N-alkylated lactams isolated were characterized as described below. 1-Methyl-2-piperidinone (**15**), a colorless oil, bp 108° (18 mmHg) [lit.[25] bp 104° (14 mmHg)]; IR ν_{max}^{film} 1630 cm^{-1} (lactam CO). This sample was identical (by TLC and IR and NMR spectra) with the one [NMR ($CDCl_3$) δ: 3.00 (3H, s, N–Me)] prepared from 1-methyl-2-pyridone[26] by catalytic reduction (Raney Ni/H_2, EtOH). 1-Ethyl-2-piperidinone (**12**), a colorless oil, identical (by TLC and IR spectrum) with a sample [bp 106—107° (17 mmHg); lit.[27] bp 120—122° (27 mmHg); IR ν_{max}^{film} 1627 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7 Hz, $NCH_2\underline{Me}$)] synthesized in 95% yield from 1-ethyl-2-pyridone[28] by catalytic hydrogenation (Raney Ni/H_2, EtOH). 1-(3,4-Dimethoxyphenethyl)-2-piperidinone (**26b**), 1-phenethyl-2-piperidinone (**25b**), and 1-benzyl-2-piperidinone (**13**) were also identified by direct comparison of their TLC mobility and IR spectra with those of authentic samples.[19a,21,29]

Reactions of the Lactim Ethers (10a—d, 11a—c) with Phenacyl Bromide and 3,4-Dimethoxyphenacyl Bromide (Step B in Chart 5) (Table II)——General Procedure: A mixture of a lactim ether (22—24 mmol) and phenacyl bromide or 3,4-dimethoxyphenacyl bromide[22] (20 mmol) in DMF (20 ml) (or without DMF) was heated at 60° for 1—6 hr. After cooling, the solvent was evaporated *in vacuo* and the residue was dissolved in benzene (200 ml). The benzene solution was washed successively with 5% aq. NaOH and H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was purified by recrystallization or column chromatography. The results with **10a—d** and **11a—c** are summarized in Table II, and the lactam ketones (**21a—d, 22a—c**) thus isolated were characterized as follows.

1-Phenacyl-2-pyrrolidinone (21a)——Recrystallized from isopropyl ether to colorless prisms, mp 70—71°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (CO), 1677 (lactam CO); NMR ($CDCl_3$) δ: 1.94—2.29 (2H, m, $H_{(4)}$'s), 2.37—2.59 (2H, m, $H_{(3)}$'s), 3.50 (2H, t, J=7 Hz, $H_{(5)}$'s), 4.73 (2H, s, $COCH_2N$), 7.35—8.05 (5H, m, Ph). *Anal.* Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.04; H, 6.36; N, 6.97.

1-Phenacyl-2-piperidinone (21b)——Crystallized from isopropyl ether in colorless plates, mp 64—65°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1698 (CO), 1630 (lactam CO); NMR ($CDCl_3$) δ: 1.72—2.12 (4H, m, $H_{(4)}$'s and $H_{(5)}$'s), 2.38—2.70 (2H, m, $H_{(3)}$'s), 3.28—3.56 (2H, m, $H_{(6)}$'s), 4.84 (2H, s, $COCH_2N$), 7.49—8.05 (5H, m, Ph). *Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.62; H, 6.86; N, 6.44.

Hexahydro-1-phenacyl-2*H*-azepin-2-one (21c)——Recrystallized from isopropyl ether to colorless plates, mp 58—59°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1699 (CO), 1633 (lactam CO); NMR ($CDCl_3$) δ: 1.52—1.88 (6H, m, $H_{(4)}$'s, $H_{(5)}$'s, and $H_{(6)}$'s), 2.42—2.72 (2H, m, $H_{(3)}$'s), 3.30—3.52 (2H, m, $H_{(7)}$'s), 4.84 (2H, s, $COCH_2N$), 7.32—8.04 (5H, m, Ph). *Anal.* Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.73; H, 7.39; N, 6.17.

5-Ethyl-1-phenacyl-2-piperidinone (21d)——Purified by column chromatography (silica gel, AcOEt) to a pale yellowish oil, MS *m/e*: 245 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1698 (CO), 1631 (lactam CO); NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 1.21—2.59 (7H, m, $C\underline{H_2}Me$, $H_{(3)}$'s, $H_{(4)}$'s, and $H_{(5)}$), 2.95—3.41 (2H, m, $H_{(6)}$'s), 4.72 and 4.89 (1H each, a pair of AB type d, J=17 Hz, $COCH_2N$), 7.35—8.05 (5H, m, Ph).

1-(3,4-Dimethoxyphenacyl)-2-pyrrolidinone (22a)——Recrystallized from hexane–AcOEt (1:1, v/v) to colorless prisms, mp 85—86°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1691 (CO), 1677 (lactam CO); NMR ($CDCl_3$) δ: 1.92—2.28 (2H,

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m, $H_{(4)}$'s), 2.36—2.60 (2H, m, $H_{(3)}$'s), 3.51 (2H, t, J=7 Hz, $H_{(5)}$'s), 3.94 and 3.96 (3H each, s, two MeO's), 4.68 (2H, s, $COCH_2N$), 6.92 (1H, d, J=8.3 Hz, $H_{(5')}$), 7.53 (1H, d, J=2 Hz, $H_{(2')}$), 7.63 (1H, d-d, J=8.3 and 2 Hz, $H_{(6')}$). *Anal.* Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.96; H, 6.45; N, 5.03.

1-(3,4-Dimethoxyphenacyl)-2-piperidinone (22b)——i) By the Lactim Ether Method: The crude product from the reaction of **10b** or **11b** with 3,4-dimethoxyphenacyl bromide (Table II) was recrystallized from hexane–AcOEt (1: 1, v/v) to colorless plates, mp 89—90°, identical (by mixed melting-point test and IR spectrum) with a sample prepared by method-(ii).

ii) By Oxidation of Lactam Alcohol **24b**: To an ice-cooled, stirred solution of lactam alcohol **24b** (1.40 g, 5 mmol), prepared according to previously reported procedure,[19a] in 25% aq. acetone (40 ml) was added portionwise $KMnO_4$ (3.95 g, 25 mmol) over a period of 10 min at such a rate that the inner temperature of the mixture did not exceed 13°. The resulting mixture was stirred at 3—5° for 4 hr, and then the brown precipitate that resulted was filtered off and washed with 25% aq. acetone (2×5 ml). The combined filtrate and washings were concentrated to a small volume (*ca.* 25 ml) and extracted with $CHCl_3$ (1×30 ml, 2×15 ml). The $CHCl_3$ extracts were washed successively with 5% aq. HCl and H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave a light brown, thick oil (1.38 g). The oil was chromatographed (alumina, AcOEt) to give **22b** (1.04 g, 82%) as a colorless solid, mp 76—82°. Recrystallization from isopropyl ether or AcOEt yielded an analytical sample as colorless plates, mp 89—90°; MS *m/e*: 277 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1688 (CO), 1630 (lactam CO); NMR ($CDCl_3$) δ: 1.70—2.10 (4H, m, $H_{(4)}$'s and $H_{(5)}$'s), 2.25—2.70 (2H, m, $H_{(3)}$'s), 3.20—3.55 (2H, m, $H_{(6)}$'s), 3.91 and 3.94 (3H each, s, two MeO's), 4.77 (2H, s, $COCH_2N$), 6.88 (1H, d, J=8.2 Hz, $H_{(5')}$), 7.33 (1H, d, J=2.2 Hz, $H_{(2')}$), 7.62 (1H, d-d, J=8.2 and 2.2 Hz, $H_{(6')}$). *Anal.* Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.84; H, 6.78; N, 5.32.

1-(3,4-Dimethoxyphenacyl)-hexahydro-2*H*-azepin-2-one (22c)——Crystallized from isopropyl ether in colorless plates, mp 95—96°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1686 (CO), 1632 (lactam CO); NMR ($CDCl_3$) δ: 1.58—1.86 (6H, m, $H_{(4)}$'s, $H_{(5)}$'s, and $H_{(6)}$'s), 2.46—2.74 (2H, m, $H_{(3)}$'s), 3.30—3.50 (2H, m, $H_{(7)}$'s), 3.92 and 3.94 (3H each, s, two MeO's), 4.80 (2H, s, $COCH_2N$), 6.87 (1H, d, J=8 Hz, $H_{(5')}$), 7.51 (1H, d, J=2 Hz, $H_{(2')}$), 7.60 (1H, d-d, J=8 and 2 Hz, $H_{(6')}$). *Anal.* Calcd. for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.87; H, 7.16; N, 4.77.

The $NaBH_4$ Reduction of the Lactam Ketones (21a—d, 22a—c) (Step C in Chart 5) (Table II)——Solutions of the lactam ketones (**21a—d**, **22a—c**) (20 mmol) in EtOH (50 ml) were separately stirred under ice-cooling and $NaBH_4$ (20 mmol) was added portionwise. The resulting mixtures were kept stirred at room temp. for 1—3 hr. The solvent was removed from these mixtures by evaporation *in vacuo* and H_2O was added to the residues. The aqueous mixtures were separately extracted with benzene. The benzene solutions were washed with H_2O, dried over anhyd. K_2CO_3, and evaporated *in vacuo* to leave the desired lactam alcohols (**23a—d**, **24a—c**) (Table II), which were characterized as described below.

1-(2-Hydroxy-2-phenylethyl)-2-pyrrolidinone (23a)——Recrystallized from hexane–AcOEt (1: 1, v/v) to colorless prisms, mp 117—118° (lit. mp 117—118°;[14] mp 116—117°[30]); IR ν_{max}^{Nujol} cm^{-1}: 3310 (OH), 1650 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360 (OH), 1665 (lactam CO); NMR ($CDCl_3$) δ: 1.72—2.11 (2H, m, $H_{(4)}$'s), 2.23—2.47 (2H, m, $H_{(3)}$'s), 3.28 (2H, t, J=7 Hz, $H_{(5)}$'s), 3.51 [2H, d, J=5.5 Hz, CH(OH)C$\underline{H}_2$N], 4.12—4.36 (1H, b, OH), 4.93 [1H, t, J=5.5 Hz, C$\underline{H}$(OH)CH_2N], 7.24—7.52 (5H, m, Ph). *Anal.* Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.12; H, 7.31; N, 6.80.

1-(2-Hydroxy-2-phenylethyl)-2-piperidinone (23b)——Crystallized from hexane–AcOEt in colorless plates, mp 112—113° (lit.[23] mp 112—113°); IR ν_{max}^{KBr} cm^{-1}: 3320 (OH), 1608 (lactam CO); NMR ($CDCl_3$) δ: 1.48—1.88 (4H, m, $H_{(4)}$'s and $H_{(5)}$'s), 2.24—2.48 (2H, m, $H_{(3)}$'s), 2.80—3.32 (2H, m, $H_{(6)}$'s), 3.76 [2H, d, J=5 Hz, CH(OH)C$\underline{H}_2$N], 4.96 [1H, t, J=5 Hz, C$\underline{H}$(OH)CH_2N], 7.32 (5H, s, Ph). This sample was identical (by mixed melting-point test and IR spectrum) with authentic **23b**.[23]

Hexahydro-1-(2-hydroxy-2-phenylethyl)-2*H*-azepin-2-one (23c)——Crystallized from isopropyl ether in colorless needles, mp 89—90° (lit. mp 88—89°;[14] mp 89—90°[31]); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (OH), 1617 (lactam CO); NMR ($CDCl_3$) δ: 1.28—1.82 (6H, m, $H_{(4)}$'s, $H_{(5)}$'s, and $H_{(6)}$'s), 2.40—2.68 (2H, m, $H_{(3)}$'s), 3.14—3.36 (2H, m, $H_{(7)}$'s), 3.58—3.74 [2H, m, CH(OH)C$\underline{H}_2$N], 4.20—4.48 (1H, b, OH), 4.90—5.06 [1H, m, C$\underline{H}$(OH)-CH_2N], 7.18—7.54 (5H, m, Ph). *Anal.* Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.94; H, 8.10; N, 5.95.

5-Ethyl-1-(2-hydroxy-2-phenylethyl)-2-piperidinone (23d)——Obtained as a slightly yellowish oil, which was presumed to be a diastereoisomeric mixture. The IR spectrum of this sample was superimposable on that of authentic **23d**.[9]

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-2-pyrrolidinone (24a)——Recrystallized from hexane–AcOEt (1: 1, v/v) to colorless prisms, mp 90—91° (dried over P_2O_5 at 40—45° and 1 mmHg overnight); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 (OH), 1666 (lactam CO); NMR ($CDCl_3$)δ: 1.74—2.16 (2H, m, $H_{(4)}$'s), 2.24—2.52 (2H, m, $H_{(3)}$'s), 3.31 (2H, t, J=7 Hz, $H_{(5)}$'s), 3.44—3.60 [2H, m, CH(OH)C$\underline{H}_2$N], 3.70—3.80 (1H, b, OH), 3.90 (6H,

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31) H. Möhrle, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **298**, 664 (1965).

s, two MeO's), 4.78—4.98 [1H, m, C<u>H</u>(OH)CH_2N], 6.74—7.02 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{14}H_{19}NO_4 \cdot 1/4H_2O$: C, 62.32; H, 7.29; N, 5.19. Found: C, 62.39; H, 7.22; N, 5.08.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-2-piperidinone (24b)——Recrystallized from AcOEt-isopropyl ether to colorless pillars, mp 106—107°, identical (by mixed melting-point test and IR spectrum) with an authentic sample.[19a)]

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-hexahydro-2*H*-azepin-2-one (24c)——A pale yellowish, thick oil, MS *m/e*: 293 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360 (OH), 1618 (lactam CO); NMR ($CDCl_3$) δ: 1.38—1.82 (6H, m, $H_{(4)}$'s, $H_{(5)}$'s, and $H_{(6)}$'s), 2.44—2.64 (2H, m, $H_{(3)}$'s), 3.18—3.34 (2H, m, $H_{(7)}$'s), 3.38—3.52 (1H, b, OH), 3.56—3.70 [2H, m, CH(OH)C<u>H_2</u>N], 3.87 and 3.89 (3H each, s, two MeO's), 4.79—4.94 [1H, m, C<u>H</u>(OH)-CH_2N], 6.70—7.02 (3H, m, aromatic protons).

Hydrogenolysis of the Lactam Alcohols (23a—d, 24a—c) to the N-(2-Arylethyl)lactams (25a—d, 26a—c) (Step D in Chart 5) (Table II)——The hydrogenolysis of **23a** to **25a** is described in detail as a typical example. The other lactam alcohols were similarly hydrogenolyzed to the corresponding lactams (see Table II), which were characterized as described below.

1-Phenethyl-2-pyrrolidinone (25a)——A solution of **23a** (1.03 g, 5.02 mmol) in EtOH (60 ml) containing 70% aq. $HClO_4$ (0.6 ml) was hydrogenated over 10% Pd-C (1.2 g) at 25° and 3.75 atmospheric pressure; one equivalent mole of H_2 was taken up within 1.5 hr. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to leave a slightly yellowish sirup. The residue was dissolved in $CHCl_3$ and the solution was washed successively with H_2O, 5% aq. NaOH, and H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to give **25a** (932 mg, 98%) as a colorless solid. Recrystallization from hexane–ether (2: 1, v/v) furnished an analytical sample as colorless prisms, mp 50—52° (lit.[32)] mp 54—55°); IR $\nu_{max}^{CHCl_3}$ 1671 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 1.73—2.11 (2H, m, $H_{(4)}$'s), 2.23—2.45 (2H, m, $H_{(3)}$'s), 2.73—2.96 (2H, m, PhC<u>H_2</u>), 3.24 (2H, t, J=7 Hz, $H_{(5)}$'s), 3.43—3.66 (2H, m, $PhCH_2C\underline{H_2}N$), 7.05—7.43 (5H, m, Ph). *Anal.* Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.05; H, 7.88; N, 7.41.

1-Phenethyl-2-piperidinone (25b)——A colorless solid, mp 36—38°, bp 150—152° (3.5 mmHg), identical (by TLC and IR spectrum) with an authentic sample.[21)]

Hexahydro-1-phenethyl-2*H*-azepin-2-one (25c)——A colorless oil, bp 154° (3 mmHg) [lit. bp 128—130° (0.05 mmHg);[32)] mp 49—50°;[32)] mp 45—46°[14)]]; MS *m/e*: 217 (M^+); IR $\nu_{max}^{CHCl_3}$ 1628 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 1.41—1.83 (6H, m, $H_{(4)}$'s, $H_{(5)}$'s, and $H_{(6)}$'s), 2.41—2.61 (2H, m, $H_{(3)}$'s), 2.73—2.95 (2H, m, PhC<u>H_2</u>), 3.17—3.33 (2H, m, $H_{(7)}$'s), 3.49—3.71 (2H, m, $PhCH_2C\underline{H_2}N$), 7.05—7.41 (5H, m, Ph).

5-Ethyl-1-phenethyl-2-piperidinone (25d)——A colorless oil, bp 164° (3 mmHg) [lit. bp 130—140° (bath) (1 mmHg);[33)] bp 170—174° (bath) (3 mmHg)[9)]], identical (by TLC and IR spectrum) with an authentic sample.[9)]

1-(3,4-Dimethoxyphenethyl)-2-pyrrolidinone (26a)——A colorless oil, bp 156° (0.02 mmHg) (lit.[34)] mp 57°); MS *m/e*: 249 (M^+); IR $\nu_{max}^{CHCl_3}$ 1672 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 1.78—2.12 (2H, m, $H_{(4)}$'s), 2.26—2.49 (2H, m, $H_{(3)}$'s), 2.70—2.92 (2H, m, ArC<u>H_2</u>), 3.29 (2H, t, J=7 Hz, $H_{(5)}$'s), 3.44—3.66 (2H, m, $ArCH_2C\underline{H_2}N$), 3.88 and 3.91 (3H each, s, two MeO's), 6.68—6.96 (3H, m,aromatic protons).

1-(3,4-Dimethoxyphenethyl)-2-piperidinone (26b)——Recrystallized from isopropyl ether to colorless plates, mp 56—57°, identical (by TLC, IR spectrum, and mixed melting-point test) with an authentic sample.[19a)]

1-(3,4-Dimethoxyphenethyl)-hexahydro-2*H*-azepin-2-one (26c)——Recrystallized from hexane–AcOEt (5: 1, v/v) to colorless prisms, mp 84—85°; IR $\nu_{max}^{CHCl_3}$ 1626 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 1.44—1.82 (6H, m, $H_{(4)}$'s, $H_{(5)}$'s, and $H_{(6)}$'s), 2.42—2.62 (2H, m, $H_{(3)}$'s), 2.69—2.91 (2H, m, ArC<u>H_2</u>), 3.21—3.39 (2H, m, $H_{(7)}$'s), 3.50—3.72 (2H, m, $ArCH_2C\underline{H_2}N$), 3.87 and 3.90 (3H each, s, two MeO's), 6.68—6.91 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.07; H, 8.22; N, 5.07.

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