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Studies on the Syntheses of Analgesics. IV.¹⁾ Syntheses of 1,2,3,4-Tetrahydro-5H-benzazepine Derivatives²⁾

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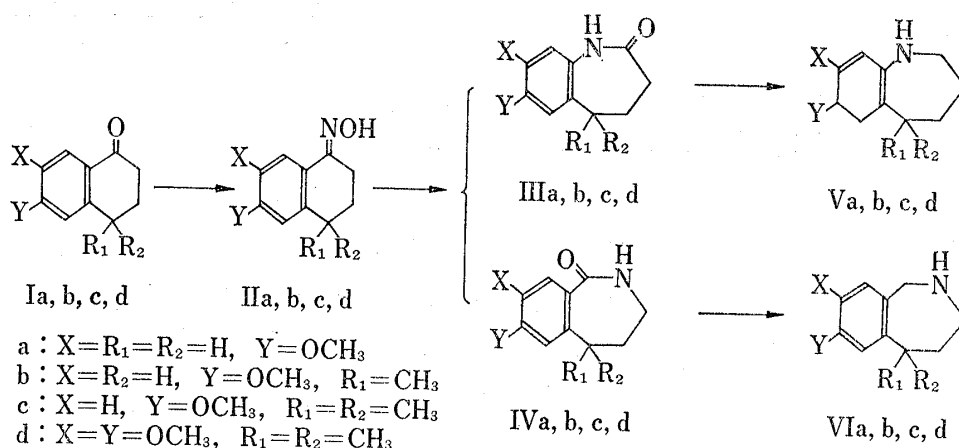
In order to examine more advantageous syntheses and the structure activity relationship, derivatives of 1,2,3,4-tetrahydro-5H-benzazepine were synthesized *via* two routes from 3,4-dihydro-1(2H)-naphthalenone. First, these compounds were synthesized *via* Beckmann rearrangement of 3,4-dihydro-1(2H)-naphthalenone oximes and second, *via* 2-(2-cyano-1,1-dimethylethyl)-4-methoxybenzoic acid. The synthesized compounds were tested for analgesic activity in mice.

In the previous paper,⁴⁾ we reported that 2-alkyl-substituted 1,2,3,4-tetrahydro-5H-2-benzazepine derivatives designed from galanthamine, an alkaloid of Amaryllidaceae, have a strong and unique analgesic activity as galanthamine. These derivatives were synthesized *via* the Bischler-Napieralski reaction of N-formyl-3-(3-methoxyphenyl)-3-methylbutylamine. As a continuation of this work, we wish to report on more advantageous syntheses and the structure-activity relationship of these 1,2,3,4-tetrahydro-5H-2-benzazepines and related compounds from 3,4-dihydro-1(2H)-naphthalenone derivatives, which could be obtained relatively easily.

3,4-Dihydro-6,7-dimethoxy-4,4-dimethyl-1(2H)-naphthalenone (Id), one of the starting materials, was initially obtained by the method of Arnold, *et al.*,⁵⁾ but later in one-step synthesis from a mixture of veratrol and dimethylbutyrolactone treated with polyphosphoric acid (PPA), in a satisfactory yield.

First, we synthesized 1,2,3,4-tetrahydro-5H-2-benzazepines *via* Beckmann rearrangement of 3,4-dihydro-1(2H)-naphthalenone derivatives (I). Earlier reports⁶⁾ have described the Beckmann rearrangement and Schmidt reaction of 3,4-dihydro-1(2H)-naphthalenone derivatives. Particularly, Minami, *et al.*^{6a)} and Uyeo, *et al.*^{6b)} reported on the Schmidt reaction of 7'-methoxy-spiro[cyclohexane-1,1'-(2'H)-naphthalene]-4(3'H)-ones. Further, Evans, *et al.*^{6c)} and Tomita, *et al.*^{6a)} also reported on the Schmidt reaction of Ia without describing the yield of the reaction product.

- 1) Part III: Y. Sawa, T. Kato, A. Morimoto, T. Masuda, M. Hori, and H. Fujimura, *Yakugaku Zasshi*, **95**, 261 (1975).
- 2) Part of this paper was presented at the 3rd International Congress of Heterocyclic Chemistry, Sendai, Aug. 1971.
- 3) Location: a) Juso-Hon-machi, Yodogawa-ku, Osaka; b) Mitahora-492-36, Gifu; c) Tsukasa-machi-40, Gifu.
- 4) M. Hori, H. Fujimura, T. Masuda, and Y. Sawa, *Yakugaku Zasshi*, **95**, 131 (1975).
- 5) P.T. Arnold, J.S. Backley, Jr., and J. Richter, *J. Am. Chem. Soc.*, **69**, 2322 (1947).
- 6) a) S. Minami, M. Tomita, I. Takamatsu, and S. Uyeo, *Chem. Pharm. Bull.* (Tokyo), **13**, 1084 (1965); b) S. Uyeo, H. Shirai, A. Koshiro, T. Yashiro, and K. Kagei, *Chem. Pharm. Bull.* (Tokyo), **14**, 1033 (1966); c) D. Evans and I.M. Lockhart, *J. Chem. Soc.*, **1965**, 4806; d) M. Tomita, S. Minami, and S. Uyeo, *J. Chem. Soc.*, **1969**, C, 183; e) L. Bauer and R.E. Hewitsen, *J. Org. Chem.*, **27**, 3982 (1962); S. Nizamuddin and D.N. Chaudhurg, *J. Indian Chem. Soc.*, **40**, 960 (1963); N.S. Hjelte and T. Agback, *Acta Chem. Scand.*, **18**, 191 (1964); P.J. Lansburg and N.R. Mancuso, *Tetrahedron Letters*, **1965**, 2445.



We investigated the Beckmann rearrangement of I from the industrial point of view because of the fact that the dangerous HN_3 was unavoidably generated during the course of the Schmidt reaction. I was converted to oxime (II) in the usual manner and II gave a mixture of lactams (III and IV) by treatment with PPA, as illustrated in Chart 1. These mixtures could be distinguished clearly by thin-layer chromatography (TLC). The R_f value of lactam III was smaller than that of IV on alumina plate (solvent system, chloroform/ethyl acetate = 4:3), *e.g.*, the R_f values of IIIa, IVa, IIIc and IVc were 0.25, 0.50, 0.28 and 0.54, respectively. III and IV, which had been separated and purified by column chromatography from a reaction mixture, were reduced, respectively, with lithium aluminum hydride in dry ether (or tetrahydrofuran) to afford the respective reduced compounds (V and VI). The structure of VIc hydrochloride was established to be 1,2,3,4-tetrahydro-7-methoxy-5,5-dimethyl-5H-2-benzazepine hydrochloride as its melting point, infrared (IR) spectrum and nuclear magnetic

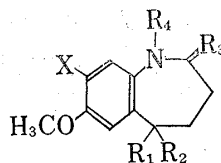
TABLE I. Physical Data of Lactams

Compound	IR (KBr) $\nu_{\text{C=O}}$ (cm^{-1})	NMR (CDCl_3) δ (ppm)						
		$\text{C}_5\text{-H}$	$\text{C}_3\text{-H}$	$\text{C}_4\text{-H}$	$\text{C}_6\text{-H}$	$\text{C}_8\text{-H}$	$\text{C}_9\text{-H}$	O-CH_3 (s)
IIIa	1672	2.77 (t)	2.0 — 2.4 (m)		6.6 — 7.1 (m)			3.80
IIIb	1670	3.05 (m)	2.0 — 2.5 (m)		6.5 — 7.1 (m)		1.31 (d)	3.80
IIIc	1670		1.9 — 2.6 (m)		6.6 — 7.3 (m)		1.40 (s)	3.98
IIId	1655		2.0 — 2.5 (m)			6.90 (s)	6.52 (s)	1.40 (s)
IVa	1660	3.18 (t)	2.85 (t)	1.98 (t)	6.6 — 7.1 (m)		7.70 (d)	3.85
IVb	1655	2.85 — 3.60 (m)		2.0 — 2.4 (m)	6.7 — 7.0 (q)		7.66 (d)	1.40 (d)
IVc	1655		3.18 (t)	1.98 (t)	6.75 — 7.10 (m)		7.55 (d)	1.42 (s)
IVd	1652		3.12 (t)	1.93 (t)		6.87 (s)	7.32 (s)	1.40 (s)
								3.90 3.92

As Minami, *et al.*^{6a)} have pointed out, it is difficult to determine the structure or the ratio of III and IV in a reaction mixture by IR spectrum only, because the absorption bands of the carbonyl group of III and IV overlap each other. But comparison of the IR spectra of the corresponding lactams, III and IV, gave some indication of the structure-confirmation;



TABLE II.



Compound	X	R ₁	R ₂	R ₃	R ₄	mp (°C)	Formula	Anal. (%)		
								Calcd.	Found	
								C	H	N
IIIa	H	H	H	O	H	143—144	C ₁₁ H ₁₃ O ₂ N	69.09 (69.30)	6.85 (6.74)	7.33 (7.22)
Va	H	H	H	H ₂	H	203—204	C ₁₁ H ₁₅ ON·HCl	61.82 (61.70)	7.55 (7.63)	6.55 (6.58)
XIXa	H	H	H	H ₂	CH ₂ C ₃ H ₅ ^{a)}	148—150	C ₁₅ H ₂₂ ON·HCl	67.02 (66.84)	8.62 (8.24)	5.21 (5.11)
IIIb	H	H	CH ₃	O	H	147.5—149.5	C ₁₂ H ₁₅ O ₂ N	70.22 (70.36)	7.37 (7.46)	6.82 (6.95)
Vb	H	H	CH ₃	H ₂	H	oil	C ₁₂ H ₁₇ ON	75.35 (74.98)	8.96 (8.72)	7.32 (7.04)
XIXb	H	H	CH ₃	H ₂	CH ₂ C ₃ H ₅ ^{a)}	144.5—146.5	C ₁₆ H ₂₃ ON·HCl	68.19 (68.02)	8.58 (8.66)	4.97 (4.81)
IIIc	H	CH ₃	CH ₃	O	H	139—142	C ₁₃ H ₁₇ O ₂ N	71.20 (71.26)	7.82 (7.70)	6.39 (6.28)
IIId	H ₃ CO	CH ₃	CH ₃	O	H	145—147	C ₁₄ H ₁₉ O ₃ N	67.45 (67.17)	7.68 (7.53)	5.62 (5.76)

a) cyclopropylmethyl

that is, generally, the absorption band of the carbonyl group of IV was observed at a lower wave number than that of III. We tried to divide the lactams, which were synthesized and separated in this work into the III and IV types by comparing the IR spectra and *R_f* values of TLC and these results agreed with those of classification by comparing the NMR spectra.

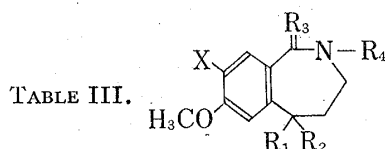
Lactams obtained from IIa, IIb and IIc were reduced with lithium aluminum hydride to afford the corresponding 1,2,3,4-tetrahydro-5H-1-benzazepine derivatives (Va, Vb and Vd) and 1,2,3,4-tetrahydro-5H-2-benzazepine derivatives (VIa, VIb and VIc), respectively. In the case of Vd and VIc, a crude product by Beckmann rearrangement of IIc was reduced immediately without purification and the resulting reaction mixture was chromatographed over silica gel giving Vd and VIc. This is more advantageous than the method with purification at the lactam stage (IIId and IVd) at the point of separation.

Synthesis of IV-type compounds by Beckmann rearrangement can not avoid the production of III. As a secondary synthetic route, we investigated the method by way of 2-(2-cyano-1,1-dimethylethyl)-4-methoxybenzoic acid (VIII) from Ic. That is, the 2-hydroxyimino compound (VII), obtained by treating Ic with isoamyl nitrite in the presence of sodium ethoxide or ethyl nitrite in the presence of hydrochloric acid in ethanol, was converted into VIII in a good yield by a ring cleavage reaction using tosyl chloride in sodium hydroxide solution. 2-(3-Amino-1,1-dimethylpropyl)-4-methoxybenzoic acid (IX), which was obtained by the reduction of VIII, was led to a closed-ring compound by dehydration, which was identified as IVc obtained from IIc.

On the other hand, VIII was heated in a mixture of ethanol and conc. sulfuric acid (1:1) for 15 hr giving about an equal mixture of amide-ester compound (XIII) and diester compound (XIV). XIII was also obtained selectively by heating VIII for 7 hr in a mixture of ethanol and conc. sulfuric acid (10:1). A reaction mixture of XIII and XIV without purification was reduced with lithium aluminum hydride in ether to afford a mixture of amino-alcohol compound (XI) and diol compound (XV). This mixture was simply separated into XI and

XV by treatment with diluted hydrochloric acid. Methyl 2-(2-cyano-1,1-dimethylethyl)-4-methoxybenzoate (X), which was obtained from VIII by passing gaseous hydrochloric acid into methanol cooling on an ice bath, was also reduced with lithium aluminum hydride to afford XI. XV was converted into the corresponding dichloride (XVI) by treatment with thionyl chloride. XVI was subjected to the ring closure reaction with tosyl amide and phenethylamine to give 1,2,3,4-tetrahydro-7-methoxy-5,5-dimethyl-2-(4-methylbenzenesulfonyl)-5H-2-benzazepine (XVII) and 1,2,3,4-tetrahydro-7-methoxy-5,5-dimethyl-2-phenethyl-5H-2-benzazepine (XVIII), respectively. In order to confirm the structure, XVII was converted into VIc by heating with conc. hydrochloric acid in a sealed tube. Treatment of XI hydrochloride with thionyl chloride gave 3-(2-chloromethyl-5-methoxyphenyl)-3-methylbutylamine (XII) and the dehydrochlorination of XII with sodium hydroxide gave VIc.

Furthermore, the following compounds were synthesized for the purpose of testing the analgesic activity. The Schotten-Baumann reaction of Va, b and VIa—c with cyclopropylcarbonyl chloride gave the corresponding amide compounds, which were reduced with lithium aluminum hydride to afford 1 (or 2)-cyclopropylmethyl-1,2,3,4-tetrahydro-7-methoxy-5H-1 (or 2)-benzazepine derivatives (XIXa, b) [or (XXa—c)], respectively. Treatment of VIc with phenethyl bromide gave 1,2,3,4-tetrahydro-7,8-dimethoxy-5,5-dimethyl-2-phenethyl-5H-2-benzazepine (XXI). Treatment of XXc with 48% hydrobromic acid under reflux gave the 7-hydroxy compound (XXII) and furthermore, XXII was acetylated to the 7-acetoxy com-



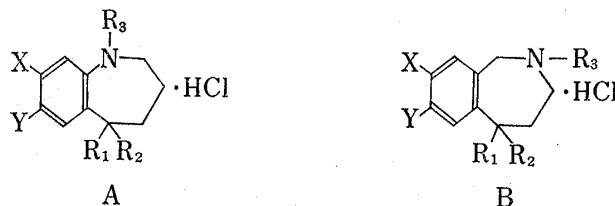
Compound	X	R ₁	R ₂	R ₃	R ₄	mp (°C)	Formula	Anal. (%)		
								Calcd.	(Found)	
								C	H	N
IVa	H	H	H	O	H	159—160	C ₁₁ H ₁₃ O ₂ N	69.09 (69.37)	6.85 6.78	7.33 7.09
VIa	H	H	H	H ₂	H	208—210	C ₁₁ H ₁₅ ON·HCl	61.82 (61.51)	7.55 7.24	6.55 6.49
XXa	H	H	H	H ₂	CH ₂ C ₃ H ₅ ^{a)}	163—165	C ₁₅ H ₂₂ ON·HCl	67.02 (66.98)	8.63 8.34	5.21 5.26
IVb	H	H	CH ₃	O	H	158—159.5	C ₁₂ H ₁₅ O ₂ N	70.22 (69.91)	7.37 7.18	6.82 6.69
VIb	H	H	CH ₃	H ₂	H	oil				
XXb	H	H	CH ₃	H ₂	CH ₂ C ₃ H ₅ ^{a)}	184—186	C ₁₆ H ₂₃ ON·HCl	68.19 (67.91)	8.58 8.47	4.97 4.86
IVc	H	CH ₃	CH ₃	O	H	145—146	C ₁₃ H ₁₇ O ₂ N	71.20 (71.20)	7.82 7.77	6.39 6.32
VIc	H	CH ₃	CH ₃	H ₂	H	164—166	C ₁₃ H ₁₉ ON·HCl· 1/3H ₂ O	63.02 (62.76)	8.41 8.68	5.65 5.56
XXc	H	CH ₃	CH ₃	H ₂	CH ₂ C ₃ H ₅ ^{a)}	162—163	C ₁₇ H ₂₅ ON·HCl	69.02 (69.13)	8.86 8.95	4.73 4.71
XVIII	H	CH ₃	CH ₃	H ₂	C ₂ H ₄ C ₆ H ₅ ^{b)}	176—178	C ₂₁ H ₂₇ ON·HCl· 1/2H ₂ O	71.07 (70.93)	8.23 8.16	3.95 4.14
IVd	H ₃ CO	CH ₃	CH ₃	O	H	167—169	C ₁₄ H ₁₉ O ₃ N	67.45 (67.31)	7.68 7.73	5.62 5.62
VIc	H ₃ CO	CH ₃	CH ₃	H ₂	H	210—212	C ₁₄ H ₂₁ O ₂ N·HCl· 1/2H ₂ O	59.88 (59.93)	8.26 8.18	4.99 5.08
XXI	H ₃ CO	CH ₃	CH ₃	H ₂	C ₂ H ₄ C ₆ H ₅ ^{b)}	209—211 ^{c)}	C ₂₂ H ₂₉ O ₂ N·HCl	70.29 (70.05)	8.04 8.02	3.73 3.71

a) cyclopropylmethyl

b) phenethyl

c) decomp.

TABLE IV. Analgesic Activity of 1,2,3,4-Tetrahydro-5H-benzazepines



Compound		Structure					Analgesic activity ED ₅₀ mg/kg, s.c.	
Type	No.	X	Y	R ₁	R ₂	R ₃	Haffner	Acetic acid stretching
A	XIXa	H	H ₃ CO	H	H	CH ₂ C ₃ H ₅ ^{a)}		>50
A	XIXb	H	H ₃ CO	H	CH ₃	CH ₂ C ₃ H ₅ ^{a)}		>50
A	XIXc	H	H ₃ CO	CH ₃	CH ₃	CH ₂ C ₃ H ₅ ^{a)}		>50
B	XXa	H	H ₃ CO	H	H	CH ₂ C ₃ H ₅ ^{a)}		>50
B	XXb	H	H ₃ CO	H	CH ₃	CH ₂ C ₃ H ₅ ^{a)}		>50
B	XXc	H	H ₃ CO	CH ₃	CH ₃	CH ₂ C ₃ H ₅ ^{a)}	9.0	8.5
B	XXII	H	HO	CH ₃	CH ₃	CH ₂ C ₃ H ₅ ^{a)}	0.62	0.32
B	XXIII ^{b)}	H	H ₃ CCOO	CH ₃	CH ₃	CH ₂ C ₃ H ₅ ^{a)}	1.64	
B	XVIII	H	H ₃ CO	CH ₃	CH ₃	CH ₂ CH ₂ C ₆ H ₅		>50
B	XXId	H ₃ CO	H ₃ CO	CH ₃	CH ₃	CH ₂ CH ₂ C ₆ H ₅		>50
B	XXIV ^{c)}	H	H ₃ CO	H	C ₆ H ₅	CH ₂ C ₃ H ₅ ^{a)}		>50
B	XXV ^{c)}	H	H ₃ CO	CH ₂ (CH ₂) ₃	CH ₂	CH ₂ C ₃ H ₅ ^{a)}		>50
Morphine							5.2	0.47
Codeine							18.5	5.5

^{a)} cyclopropylmethyl^{b)} oxalate^{c)} M. Hori, H. Fujimura, T. Masuda, and Y. Sawa, *Yakugaku Zasshi*, **95**, 131 (1975)

pound (XXIII). The synthesized benzazepine derivatives in this work were tabulated in Tables II and III.

Analgesic activity of these compounds was estimated by the Haffner method and the acetic acid stretching-inhibiting method using a group which consisted of 10 mice of dd-system. These results were tabulated in Table IV. When ED₅₀ was more than 50 mg/kg, further investigation was not undertaken. XXII showed the strongest analgesic activity, which was 8.4 times that of morphine. The 7-acetoxy derivative (XXIII) of XXII showed slightly less activity than XXII but was stronger than morphine. The 7-methoxy compound (XXc) showed the same activity as codeine. Other compounds did not show analgesic activity, even if 50 mg/kg was administrated. The structure-activity relationship of 1,2,3,4-tetrahydro-5H-benzazepine derivatives is as follows: (1) Nitrogen must be in the 2-position in order to show analgesic activity. The compound which has nitrogen in the 1-position has no activity. (2) The carbon at the 5-position must be quaternary. In particular, compounds substituted with the dimethyl group have analgesic activity but those with a spiro compound at the 5-position weak activity. (3) The order of activity, decided by the substituted group at the 7-position, is HO->CH₃COO->CH₃O-.

Experimental⁷⁾

4-(3,4-Dimethoxyphenyl)-4-methylpentanoic Acid—A solution of 30 g of dimethylbutyrolactone and 96 g of veratrole in 60 ml of CS₂ was added dropwise to a stirring and ice-cooling suspension of 80 g of pul-

7) All melting points were uncorrected. IR spectra were obtained with a Hitachi EPI-S2 spectrophotometer and NMR spectra were determined on a Hitachi Perkin-Elmer R-20 spectrometer with tetramethylsilane as internal standard.

verized anhyd. AlCl_3 in 200 ml of CS_2 . The mixture was stirred at room temperature for 3 hr and then heated under reflux for 5 hr. To a stirring and cooling reaction mixture was added dropwise 10% HCl (300 ml). The organic layer was separated. The aqueous layer was extracted with ether. The combined organic solution was washed with water, dried over MgSO_4 , and concentrated. The residual oil distilled to give 4-(3,4-dimethoxyphenyl)-4-methylpentanoic acid as colorless oil (44.1 g, 66.3%), bp 180–192° (2 mmHg). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1710 (COOH). Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_4$: C, 66.64; H, 7.99. Found: C, 66.54; H, 7.99.

3,4-Dihydro-6,7-dimethoxy-4,4-dimethyl-1(2H)-naphthalenone (Id)—a) To PPA prepared from 13 ml of 85% H_3PO_4 and 35 g of P_2O_5 , 12 g of 4-(3,4-dimethoxyphenyl)-4-methylpentanoic acid was added with stirring at 80°. After additional stirring for 0.5 hr, the reaction mixture was added into a mixture of crushed ice and water. After standing for overnight, the aqueous solution was extracted with ether. The ethereal extract was washed with water, dried over MgSO_4 and evaporated to dryness. The residue was distilled *in vacuo*, bp 145–147° (0.4 mmHg), mp 68–70° (from EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1660 (CO). NMR (CDCl_3) δ : 1.40 (6H, s, $2 \times \text{C}-\text{CH}_3$), 1.88 (2H, t, C_3-H_2), 2.53 (2H, t, C_2-H_2), 3.90 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.82 (1H, s, aromatic proton), 7.53 (1H, s, aromatic proton).

b) To 400 g of PPA heated at 70°, 32.6 g of veratrole and 27 g of 4,4-dimethylbutyrolactone were added with stirring all at once. After heating at 95° for 1 hr, the reaction mixture was added into a mixture of crushed ice and water. The aqueous solution was extracted with CHCl_3 . The extract was washed with water, dried, and concentrated. The residue was distilled *in vacuo*, yield 32.6 g (59.0%) of Id. Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_3$: C, 71.77; H, 7.74. Found: C, 71.58; H, 7.92.

Preparation of 3,4-Dihydro-1(2H)-naphthalenone Oximes—To a solution of the appropriate substituted 3,4-dihydro-1(2H)-naphthalenone (0.08 mole)⁸⁻¹⁰ in 60 ml of EtOH, was added a solution of 6.7 g of $\text{NH}_2\text{OH}\cdot\text{HCl}$ and 13.3 g of sodium acetate in 25 ml of water with stirring. The solution was heated under reflux for 2 hr. On cooling, the precipitated solids were collected by filtration, washed with water, and dried.

3,4-Dihydro-6-methoxy-1(2H)-naphthalenone Oxime (IIa): 98.0%, mp 132.5–134°. Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.98; H, 6.78; N, 7.35.

3,4-Dihydro-6-methoxy-4-methyl-1(2H)-naphthalenone Oxime (IIb): 90.0%, mp 94–96°. Anal. Calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_2\text{N}$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.98; H, 7.45; N, 6.80.

3,4-Dihydro-6-methoxy-4,4-dimethyl-1(2H)-naphthalenone Oxime (IIc): 99.8%, mp 117–119°. Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{N}$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.03; H, 7.78; N, 6.41.

3,4-Dihydro-6,7-dimethoxy-4,4-dimethyl-1(2H)-naphthalenone Oxime (IId): 96.4%, mp 135–137°. Anal. Calcd. for $\text{C}_{14}\text{H}_{19}\text{O}_3\text{N}$: 67.45; H, 7.68; N, 5.62. Found: C, 67.55; H, 7.71; N, 5.54.

General Procedure for the Beckmann Rearrangement of 3,4-Dihydro-1(2H)-naphthalenone Oximes (II)—A stirred mixture of the oxime (a g) and PPA ($30 \times a$ g) was stirred at 120–130° for 10 minutes. It was then cooled to 60° and poured into a mixture of crushed ice and water. The solution was neutralized with 10% aqueous Na_2CO_3 and extracted with CHCl_3 . The extract was washed with water, dried, and concentrated *in vacuo* to give a solid of crude lactams (III and IV).

1,2,3,4-Tetrahydro-7-methoxy-5H-1 (or 2)-benzazepin-2 (or 1)-one (IIIa or IVa)—Treatment of 64.0 g of IIa with PPA according to the general procedure gave 51 g of crude lactams, mp 130–145°. Recrystallization from benzene/petroleum ether gave 26 g of IVa as colorless crystals, mp 159–160°. The mother liquor was concentrated to dryness. The residue (25 g) was chromatographed on silica gel (100–200 mesh, 250 g) with $\text{CHCl}_3/\text{AcOEt}$ (1:1). The first eluate gave 17.6 g (27.5%) of IIIa, mp 143–144° (from EtOH/petroleum benzene). The second eluate gave 7.4 g of IVa. The over-all yield of IVa was 33.4 g (52.2%).

1,2,3,4-Tetrahydro-7-methoxy-5-methyl-5H-1 (or 2)-benzazepin-2 (or 1)-one (IIIb or IVb)—Treatment of IIb (13.1 g) with PPA according to the general procedure gave 10.6 g of the solid, which was chromatographed on silica gel (100 g). The column was treated with $\text{CHCl}_3/\text{AcOEt}$ (5:4). The first compound was recrystallized from AcOEt to give 4.4 g (33.6%) of IIIb as colorless needles, mp 147.5–149.5°. The second compound was a mixture of IIIb and IVb (1.6 g) and the third compound was recrystallized from AcOEt to give 3.8 g (29.0%) of IVb as colorless plates, mp 158–159.5°.

1,2,3,4-Tetrahydro-7-methoxy-5,5-dimethyl-5H-1 (or 2)-benzazepin-2 (or 1)-one (IIIc or IVc)—Treatment of 17.6 g of IIc with PPA according to the general procedure gave 12.0 g of the solid, which was absorbed on a column of silica gel (120 g). The column was treated with $\text{CHCl}_3/\text{AcOEt}$ (1:1). The first compound eluted and recrystallized from AcOEt to give 2.4 g (13.6%) of IIIc, mp 139–142°. The second compound was eluted from the column to give 3.0 g (17.0%) of a mixture of IIIc and IVc. The third compound was eluted and recrystallized from AcOEt to give 6.5 g (36.9%) of IVc, mp 145–146°.

1,2,3,4-Tetrahydro-7,8-dimethoxy-5,5-dimethyl-5H-1 (or 2)-benzazepin-2 (or 1)-one (IIId or IVd)—Treatment of 2.6 g of IId with PPA according to the general procedure gave 2.1 g (80.8%, mp 115–135°) of

- 8) S.N. Ananchenko, V. Ye Limanov, V.N. Leonov, V.N. Rzhaznikov, and I.V. Torgov, *Tetrahedron*, **18**, 1355 (1962).
- 9) A.R. Martin, A.P. Parulkar, D.J. Gusseck, Le Ray J. Anderson, G.L. Grunewald, and A.I. White, *J. Pharm. Sci.*, **58**, 340 (1969).
- 10) G.S. Krishna Rao and Sukh Dev, *J. Indian Chem. Soc.*, **34**, 255 (1957).

the solid, which was adsorbed on a column of silica gel (60 g). The column was treated with CHCl_3 . The first compound was eluted to give 0.3 g (11.5%) of IIIId, mp 145—147° and the second compound was eluted to give 0.5 g of a mixture of IIIId and IVd. The third compound was eluted to give 0.45 g (17.0%) of IVd, mp 167—169°.

Reduction of 1,2,3,4-Tetrahydro-5H-benzazepinones (III or IV)—A suspended solution of III (or IV) (0.08 mole) and 4.7 g of lithium aluminum hydride in 250 ml of dry ether (or tetrahydrofuran) was heated under reflux for 3—10 hr. After cooling, the excess reagent was destroyed by cautious addition of 70 ml of saturated aqueous NH_4Cl . The precipitate was filtered off and washed with ether. The filtrate and the washings were combined and washed with saturated aqueous NH_4Cl , and extracted with 10% HCl . The acidic extract was made basic with NaOH and the alkaline solution was extracted with ether. The ethereal extract was washed with water, dried and evaporated to afford 1,2,3,4-tetrahydro-5H-benzazepines (V or VI) as an oil. V (or VI) hydrochloride was recrystallized from AcOEt/MeOH (Tables II and III).

Reduction of a Mixture of Lactams (IIIb and IVb)—A solution of 3.8 g of lactams (IIIb and IVb) prepared by the Beckmann rearrangement of IIb in 50 ml of tetrahydrofuran was added dropwise into a suspended solution of 2.0 g of lithium aluminum hydride in 150 ml of tetrahydrofuran at room temperature during 0.5 hr. The mixture was refluxed for 4 hr with stirring. After cooling, the excess reagent was destroyed by cautious addition of saturated aqueous NH_4Cl and the precipitate was filtered off and washed with tetrahydrofuran. The filtrate and washings were combined, washed with water and evaporated *in vacuo* to give 3.0 g of the residue, which was adsorbed on a column of silica gel (30 g). The first compound was eluted with CHCl_3 to give 1.5 g of 1,2,3,4-tetrahydro-7-methoxy-5-methyl-5H-1-benzazepine (Vb) as an oil. The second compound was eluted with $\text{CHCl}_3/\text{AcOEt}$ (1:1) to recover 0.2 g of a mixture of lactams (IIIb and IVb). The third compound was eluted with MeOH to give 1.3 g of 1,2,3,4-tetrahydro-7-methoxy-5-methyl-5H-2-benzazepine (Vib).

3,4-Dihydro-2-hydroxyimino-6-methoxy-4,4-dimethyl-1(2H)-naphthalenone (VII)—a) To an ice-cold and stirred solution of sodium methoxide prepared from 15 g of Na and 150 ml of MeOH was added a solution of 50 g of Ic in 50 ml of MeOH . The stirring mixture was added 45.5 g of isoamyl nitrite at 0—15°. The deep greenish solution was turned to brown, and then solidified. After standing at 0° for 16 hr, the mixture was decomposed with ice-water (500 ml) and washed with ether. The aqueous layer was neutralized with 10% HCl . The precipitate was collected, washed with water, and dried to give 45.5 g (77.7%) of VII, mp 172—175° (decomp.). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_3\text{N}$: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.66; H, 6.71; N, 6.14.

b) To an ice-cold and stirring solution of 14 g of Ic in 110 ml of EtOH was added 2—3 drops of conc. HCl and dropwise a solution of 8.2 g of ethyl nitrite¹¹⁾ in 25 ml of EtOH . The mixture was stirred at room temperature for 2 hr. After standing at 0° for 16 hr, the precipitate was collected. The mother liquor was evaporated, chilled, and the second precipitate was collected. The combined precipitates were washed with water and dried to give 14 g (80.7%) of VII, mp 173—175° (decomp.).

2-(2-Cyano-1,1-dimethylethyl)-4-methoxybenzoic Acid (VIII)—A cold and stirred solution of 14 g of VII in 110 ml of aqueous NaOH (10 g) was added dropwise a solution of 25.5 g of tosyl chloride in 90 ml of benzene at 15—18° during 1.5 hr and stirred at room temperature for an additional 2 hr. The benzene layer was extracted with 10% aqueous NaOH . The combined aqueous layers were neutralized with 10% HCl . The precipitate was collected, washed with water, and dried to give 11.4 g (81.4%) of VIII, which was recrystallized from benzene/ligroin, mp 130—131°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2230 (CN), 1680 (COOH). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_3\text{N}$: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.84; H, 6.52; N, 5.97.

2-(3-Amino-1,1-dimethylpropyl)-4-methoxybenzoic Acid (IX)—A suspended solution of 2.5 g of VIII, 1.2 ml of conc. HCl , 0.22 g of PtO_2 , 25 ml of water and 125 ml of EtOH was hydrogenated at room temperature. The reaction mixture was filtered and concentrated *in vacuo* to give 2.9 g of IX· HCl , which was recrystallized from AcOEt/MeOH as a colorless needles, mp 158—159°. *Anal.* Calcd. for $\text{C}_{13}\text{H}_{19}\text{O}_3\text{N}\cdot\text{HCl}$: C, 57.04; H, 7.36; N, 5.11. Found: C, 57.24; H, 7.55; N, 5.08.

1,2,3,4-Tetrahydro-7-methoxy-5,5-dimethyl-5H-2-benzazepine-1-one (IVc)—To a solution of 2 g of IX· HCl in 2 ml of water was added a solution of 1.1 g of $\text{AcONa}\cdot 3\text{H}_2\text{O}$ in 3 ml of water and evaporated *in vacuo* to dryness. The residue was taken up with EtOH , evaporated, and then melted at 235° for 7 minutes. After cooling, the solid was extracted with benzene. The extract was concentrated and the residue was chromatographed over alumina, and fractions were evaporated to give IVc, which was recrystallized from AcOEt as a colorless plates, mp 145—146°, and identified with an authentic sample.

3-(2-Hydroxymethyl-5-methoxyphenyl)-3-methylbutanol (XV)—To a solution of 10 g of VIII in 132 g of EtOH was added 140 g of conc. H_2SO_4 and heated under reflux for 15 hr. The reaction mixture was poured into a mixture (1 kg) of crushed ice and water and then extracted with CHCl_3 . The extract was washed successively with 2% aqueous NaOH and water, dried, and evaporated *in vacuo* to give 11 g of the mixture of ethyl 2-(2-carbamoyl-1,1-dimethylethyl)-4-methoxybenzoate (XIII) and ethyl 3-(2-ethoxycarbonyl-5-methoxyphenyl)-3-methylbutyrate (XIV). IR $\nu_{\text{max}}^{\text{NaCl}}$ cm^{-1} : 1680 (CONH), 1725 (COOEt). A suspended solution

11) W.L. Senion and V.R. Damerell, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, N.Y., 1943, p. 204.

of this residue, 4.5 g of lithium aluminum hydride in 100 ml of dry ether was heated under reflux for 7 hr. After cooling, the excess reagent was decomposed by cautious addition of saturated aqueous NH_4Cl . The reaction mixture was acidified with HCl and extracted with ether. The ethereal extract was washed with water, dried, and concentrated *in vacuo* to give the residual oil of XV, which was distilled under reduced pressure, bp 140–145° (1 mmHg). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{20}\text{O}_3$: C, 69.61; H, 8.99. Found: C, 69.70; H, 9.11. The acidic aqueous solution was made basic with 10% aqueous NaOH and the alkaline solution was extracted with ether. The extract was washed with water, dried over K_2CO_3 , and concentrated *in vacuo* to give XI (picrate: mp 158°). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{21}\text{O}_2\text{N} \cdot \text{C}_6\text{H}_3\text{O}_7\text{N}_3$: C, 50.44; H, 5.35; N, 12.38. Found: C, 50.69; H, 5.55; N, 12.30.

3-(2-Chloromethyl-5-methoxyphenyl)-3-methylbutyl Chloride (XVI)—To an ice-cold and stirred solution of 2.0 g of XV and 2.3 g of N,N -dimethylaniline in 30 ml of CHCl_3 was added dropwise a solution of 2.4 g of SOCl_2 in 5 ml of CHCl_3 . The mixture was cautiously heated under reflux for 3 hr. After cooling, the reaction mixture was poured into a mixture of crushed ice and water containing 2N HCl and extracted with CHCl_3 . The extract was washed with water, dried, and evaporated *in vacuo* to give XVI, bp 115–120° (2 mmHg). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{15}\text{OCl}_2$: C, 59.78; H, 6.95. Found: C, 59.61; H, 7.01.

Methyl 2-(2-Cyano-1,1-dimethylethyl)-4-methoxybenzoate (X)—a) An ice-cold and stirred solution of 10 g of VIII in 200 ml of MeOH was saturated with gaseous HCl . The solution was heated under reflux for 1 hr and evaporated *in vacuo* to give X, which was distilled, bp 183–187° (6.5 mmHg). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{17}\text{O}_3\text{N}$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.21; H, 6.78; N, 5.62.

b) A mixture of 3 g of VIII and 15 ml of purified SOCl_2 was refluxed gently on the water bath for 2 hr. The excess SOCl_2 was evaporated *in vacuo*. To an ice-cold and stirred MeOH containing K_2CO_3 (5 g) was added dropwise a solution of the residue in dry benzene. After gently heating for 1 hr, the reaction mixture was concentrated *in vacuo*. The residue was poured into water and the solution was made basic with aqueous NaOH , and extracted with ether. The extract was washed with water, dried, and concentrated *in vacuo* to give 3.0 g of the residual oil of crude X. Distillation of the residue gave 2.1 g of X, bp 183–187° (6.5 mmHg).

2-(3-Amino-1,1-dimethylpropyl)-4-methoxybenzyl Alcohol (XI)—a) A solution of 1 g of VIII and 1 ml of conc. H_2SO_4 in 12 ml of EtOH was heated under reflux for 7 hr. The reaction mixture was concentrated to one-half of its initial volume, poured into a mixture of crushed ice and water, and extracted with CHCl_3 . The extract was washed with successive, 5% aqueous Na_2CO_3 and water, dried and evaporated *in vacuo* to give 0.9 g of XIII as an oily product. The mixture (0.1 g) of VIII and XIII was obtained from the aqueous Na_2CO_3 described above. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1680 (CONH), 1725 (COOEt). The solution of 0.9 g of the oily XIII in 9 ml of dry ether was added dropwise into the stirred suspension of 0.38 g of lithium aluminum hydride in 25 ml of dry ether and the mixture was refluxed with stirring for 7 hr. After cooling, the excess reagent was destroyed by cautious addition of AcOEt and water and the ethereal layer was separated off. The aqueous layer was extracted with ether. The combined ethereal layers were washed with water, dried, and concentrated to give 0.9 g of the oily residue, which was chromatographed on silica gel. The first elution with benzene/ MeOH (1:1) gave XIII (0.2 g). The second elution gave 0.66 g (70%) of the purposed product (XI), mp 82–83°. XI picrate was recrystallized from EtOH as a colorless needles, mp 158°. *Anal.* Calcd. for $\text{C}_{13}\text{H}_{21}\text{O}_2\text{N} \cdot \text{C}_6\text{H}_3\text{O}_7\text{N}_3$: C, 50.44; H, 5.35; N, 12.38. Found: C, 50.15; H, 5.58; N, 12.17.

b) A suspended solution of 4.3 g of X and 3 g of lithium aluminum hydride in 150 ml of dry ether was heated under reflux for 20 hr. The excess reagent was decomposed by cautious addition of AcOEt and saturated aqueous NH_4Cl . The precipitate was filtered off and washed with ether. The filtrate and the washings were combined and concentrated *in vacuo* to give a residue, which was taken in CHCl_3 . The CHCl_3 solution was extracted with 5% HCl . The acidic extract was made basic with 5% aqueous NaOH and extracted with ether. The ethereal extract was washed with water, dried over K_2CO_3 , and evaporated to afford an oily XI (picrate: mp 157–158°). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{21}\text{O}_2\text{N} \cdot \text{C}_6\text{H}_3\text{O}_7\text{N}_3$: C, 50.44; H, 5.35; N, 12.38. Found: C, 50.39; H, 5.51; N, 12.44.

3-(2-Chloromethyl-5-methoxyphenyl)-3-methylbutylamine (XII)—To an ice-cold and stirred mixture of 5.2 g of XI· HCl and 25 ml of CHCl_3 was added dropwise a solution of 5.0 g of SOCl_2 in 5 ml of CHCl_3 . Then, the mixture was kept at room temperature for 3 hr. The reaction mixture was evaporated *in vacuo* to dryness and washed with petroleum ether. After treating with charcoal, a solution of the residue in CHCl_3 was evaporated *in vacuo* to give XII· HCl as a slight yellowish powdery crystals, mp 138–139°. *Anal.* Calcd. for $\text{C}_{13}\text{H}_{20}\text{ONCl} \cdot \text{HCl}$: C, 56.12; H, 7.61; N, 5.03. Found: C, 56.00; H, 7.50; N, 5.12.

1,2,3,4-Tetrahydro-7-methoxy-5,5-dimethyl-2-(4-methylbenzenesulfonyl)-5H-2-benzazepine (XVII)—A suspended solution of 2.6 g of XVI, 1.7 g of 4-toluenesulfonamide, and 4.1 g of K_2CO_3 in 100 ml of butanol was refluxed with stirring for 10 hr. After cooling, the precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was poured into water and extracted with ether. The extract was washed with water and evaporated to dryness. The residual mass was recrystallized from ether as a colorless needles, mp 128°. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{25}\text{O}_3\text{NS}$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.80; H, 7.11; N, 3.87.

1,2,3,4-Tetrahydro-7-methoxy-5,5-dimethyl-5H-2-benzazepine (VIc)—a) A cold solution of 2.8 g of XII· HCl in 30 ml of 5% aqueous NaOH was heated on the water bath for 15 minutes. The reaction mixture

was then steam distilled. The distillate was made acidic with HCl and concentrated *in vacuo* to 15 ml. The solution was made strong basic with aqueous NaOH, extracted with ether. The extract was washed with water, dried over K_2CO_3 , and evaporated to give the residue of VIc as an oily product. The picrate of VIc was recrystallized from EtOH as a slight yellowish needles, mp 200°. *Anal.* Calcd. for $C_{13}H_{19}ON \cdot C_6H_3O_7N_3$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.31; H, 5.40; N, 12.74.

b) A solution of 3 g of XVII in 100 ml of conc. HCl was heated at 130° in a sealed tube for 4 hr. The reaction mixture was made basic with aqueous NaOH and extracted with ether. The ethereal extract was washed with water, dried, and evaporated *in vacuo* to give VIc (picrate: mp 200°) as a colorless oily product. *Anal.* Calcd. for $C_{13}H_{19}ON \cdot C_6H_3O_7N_3$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.33; H, 5.25; N, 13.06.

1,2,3,4-Tetrahydro-7-methoxy-5,5-dimethyl-2-phenethyl-5H-2-benzazepine (XVIII)—a) A suspended solution of 2.6 g of XVI, 1.2 g of phenethyl bromide and 4.1 g of K_2CO_3 in 100 ml of butanol was heated under reflux for 24 hr. After cooling, the precipitate was filtered off. The filtrate was acidified with HCl, and concentrated *in vacuo*. The residue was diluted with water, and washed with ether. The aqueous layer was made basic with aqueous NaOH and extracted with ether. The extract was washed with water, dried, and concentrated to give an oily product of XVIII. XVIII·HBr was recrystallized from acetone as a colorless needles, mp 186°. *Anal.* Calcd. for $C_{21}H_{27}ON \cdot HBr$: C, 64.61; H, 7.23; N, 3.59. Found: C, 64.60; H, 7.13; N, 3.50.

b) A suspended solution of 2.0 g of VIc, 1.9 g of phenethyl bromide, and 20 g of K_2CO_3 in 100 ml of dimethylformamide was heated under reflux for 5 hr. After cooling, the precipitate was filtered off. The filtrate was evaporated *in vacuo*. The residue was diluted with water, and extracted with ether. The ethereal extract was extracted with 10% HCl and the acidic solution was neutralized with 10% NH_4OH , extracted with ether, washed with water, dried, and concentrated to give an oily residue of XVIII. This residue was changed in a usual manner to XVIII·HBr, mp 185—186°.

c) To a stirred suspended solution of 2.0 g of VIc and 4.8 g of K_2CO_3 in 60 ml of 75% aqueous MeOH was added dropwise 3.0 g of phenylacetyl chloride. After stirring for 1 hr, the solution was diluted with water and extracted with ether. The extract was washed successively with dil. HCl, dil. $NaHCO_3$, and water, dried, and evaporated to dryness. The solution of the residual oil in 20 ml of ether was added dropwise into stirred suspension of 1.2 g of lithium aluminum hydride in 100 ml of ether at room temperature. The mixture was refluxed for 8 hr with stirring. After cooling, the excess reagent was decomposed by cautious addition of saturated aqueous NH_4Cl . The ether layer was separated and aqueous layer was extracted with ether. The combined ether layers were washed successively with dil. aqueous NaOH, and water, dried and evaporated to dryness. This residual crude XVIII was changed in a usual manner to XVIII·HCl, mp 176—178°. *Anal.* Calcd. for $C_{21}H_{27}ON \cdot HCl \cdot 0.5H_2O$: C, 71.06; H, 8.23; N, 3.95. Found: C, 70.81; H, 8.10; N, 4.17.

2-Cyclopropylmethyl-1,2,3,4-tetrahydro-7-methoxy-5H-benzazepines (XIX and XX)—A solution of 0.036 mole of V (or VI) in 60 ml of MeOH was added a solution of 15.6 g of K_2CO_3 in 3 ml of water at 50°. After cooling below 10°, the mixture was added dropwise 8.0 g (0.077 mole) of cyclopropylcarbonyl chloride and stirred at room temperature for 3 hr. The precipitate was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 250 ml of tetrahydrofuran and dried over K_2CO_3 . This solution was reduced with 4.2 g (0.11 mole) of lithium aluminum hydride in 100 ml of refluxing tetrahydrofuran for 4 hr. The excess reagent was decomposed by cautious addition of 7 ml of AcOEt and 300 ml of brine. The precipitate was filtered off and the filtrate was extracted with CH_2Cl_2 . The extract was dried over K_2CO_3 , and evaporated *in vacuo* to afford XIX (or XX) as an oil. The HCl salt was recrystallized from AcOEt/MeOH (20:1). (Tables II and III).

1,2,3,4-Tetrahydro-7,8-dimethoxy-5,5-dimethyl-2-phenethyl-5H-2-benzazepine (XXI)—A suspended solution of 1.0 g of VId, 0.95 g of phenethyl bromide, and 9 g of $NaHCO_3$ in 40 ml of dimethylformamide was heated under reflux for 5 hr. The precipitate was filtered off. The filtrate was concentrated *in vacuo* and the residual oil was dissolved in 10% HCl and washed with ether. The acidic aqueous layer was made basic with 10% aqueous NaOH, and extracted with ether. The ethereal extract was washed with water, dried over K_2CO_3 , and concentrated *in vacuo* to afford XXI as an oil, which was adsorbed on a column of silica gel. The first compound was eluted with AcOEt/benzene (1:1) to give XXI, mp 50—52°. *Anal.* Calcd. for $C_{22}H_{29}O_2N$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.57; H, 8.73; N, 3.99. XXI·HCl was recrystallized from AcOEt/MeOH (1:1), mp 210—211°. Yield: 0.85 g (59.0%).

2-Cyclopropylmethyl-1,2,3,4-tetrahydro-7-hydroxy-5,5-dimethyl-5H-2-benzazepine (XXII)—A solution of 2.96 g of XXc·HCl in 20 ml of 47% HBr was heated at 130—140° for 2.5 hr. The solution was then concentrated *in vacuo* and the residue was diluted with water. The aqueous solution was made basic with 10% NH_4OH , and extracted with ether. The ethereal extract was washed with water and concentrated *in vacuo* to give 1.8 g (63.9%) of XXII as a yellowish oil. XXII·HCl was recrystallized from AcOEt/MeOH, mp 204—205°. *Anal.* Calcd. for $C_{16}H_{23}ON \cdot HCl$: C, 68.19; H, 8.58; N, 4.97. Found: C, 68.15; H, 8.59; N, 5.00.

7-Acetoxy-2-cyclopropylmethyl-1,2,3,4-tetrahydro-5,5-dimethyl-5H-2-benzazepine (XXIII)—A solution of 1.2 g of XXII in 30 ml of acetic anhydride and 90 ml of pyridine was stirred at room temperature for 2 hr. The solution was concentrated *in vacuo*. A solution of the residue in 100 ml of benzene was washed with cold

10% aqueous Na_2CO_3 and water, and dried. The filtrate was concentrated to give an oily XXIII, which gave 0.92 g (55.8%) of the crystalline oxalate, mp $176\text{--}177^\circ$. *Anal.* Calcd. for $\text{C}_{18}\text{H}_{25}\text{O}_2\text{N} \cdot \text{C}_2\text{H}_2\text{O}_4$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.77; H, 7.22; N, 3.58.

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