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Synthesis of Methylpyridine Derivative. XXXI.[1] Reaction of Acetoacetamide with α,β-Unsaturated Ketones and Aldehydes[2]

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Reaction of Acetoacetamide (I) with α,β-unsaturated ketone (II) and aldehyde (XV) is described. Reaction of I with 3-buten-2-one (IIa) gives rise to 3-carbamoyl-2,6-heptanedione (IIIa), 2-carbamoyl-5-hydroxy-5-methylcyclohexanone (IVa), 6-carbamoyl-3-methyl-2-cyclohexanone (Va), 3-acetyl-6-methyl-3,4-dihydro-2(1H)-pyridone (VIa), and 3,9-dimethyl-2-azaspiro[5,5]undeca-3,8-diene-1,7-dione (VII). Reaction conditions such as catalyst and reaction temperature influence the product formed.

Similarly, reactions of I with 3-penten-2-one (IIb), 4-methyl-3-penten-2-one (IIc), 4-phenyl-3-buten-2-one (IId), and 2-benzylideneacetophenone (IIe) afford the corresponding cyclohexanone derivatives (Vb,c,d,e) besides the dihydropyridone derivatives (VIb, d,e).

α,β-Unsaturated aldehyde such as crotonaldehyde (XVa) reacts with I to give 3-acetyl-6-hydroxy-4-methyl-2-piperidone (XVIa), 3-acetyl-4-methyl-3,4-dihydro-2(1H)-pyridone (XVIIa), and 3-acetyl-6-ethoxy-4-methyl-2-piperidone (XVIIIa). Similar reaction of cinnamaldehyde (XVb) with I gives rise to the adduct (XVIb), dihydropyridone derivative (XVIIb), and piperidone derivative (XVIIIb).

In the previous paper of this series,[4] we have reported that acetoacetamide (I) reacts with α,β-unsaturated ester such as ethyl acrylate to give 3-acetylglutarimide. This reaction involves Michael addition of the active methylene of acetoacetamide (I) to ethyl acrylate followed by ring-closure to give glutarimide derivative. The present paper reports a continuation of our studies of the reaction of acetoacetamide (I), which is most readily prepared from diketene and ammonia, with α,β-unsaturated ketones and aldehydes.

Reaction with α,β-Unsaturated Ketones

When acetoacetamide (I) was allowed to react with 3-buten-2-one (IIa) in ethanol in the presence of triethylamine at room temperature, 3-carbamoyl-2,6-heptanedione (IIIa) was obtained in 57% yield. When the reaction was carried out under reflux, 6-carbamoyl-3-methyl-2-cyclohexenone (Va) and 3-acetyl-3,4-dihydro-6-methyl-2(1H)-pyridone (VIa) were obtained in 22% and 6% yield, respectively. A similar reaction in which sodium ethoxide was used as a catalyst in place of triethylamine afforded VIa, 2-carbamoyl-5-hydroxy-5-

1) Part XXX: T. Kato, Y. Yamamoto, and M. Kondo, *Chem. Pharm. Bull.* (Tokyo), **23**, 1873 (1975).
2) This forms Part LXXI of "Studies on Ketene and Its Derivatives" by T. Kato.
3) Location: *Aobayama, Sendai, 980, Japan.*
4) T. Kato and M. Noda, *Chem. Pharm. Bull.* (Tokyo), **22**, 2947 (1974).

methylcyclohexanone (IVa), and 3,9-dimethyl-2-azaspiro[5,5]undeca-3,8-diene-1,7-dione (VII) in 8%, 2%, and 5% yield, respectively.

These structures, IIIa—VII were assigned on the basis of elemental analysis, infrared (IR) and nuclear magnetic resonance (NMR) spectral data, which are described in experimental section. Treatment of IIIa with sodium ethoxide gave rise to IVa, which was converted to Va by treatment with conc. hydrochloric acid.

Hydrolysis of Va with conc. hydrochloric acid, gave 3-methyl-2-cyclohexenone (VIII).[5] Dehydrogenation of Va with Pd-charcoal gave rise to 4-methylsalicylamide (IX), which was hydrolyzed with conc. KOH to give 4-methylsalicylic acid (X).[6]

Reaction of VIa with chloranil afforded 3-acetyl-6-methyl-2(1H)-pyridone (XI).

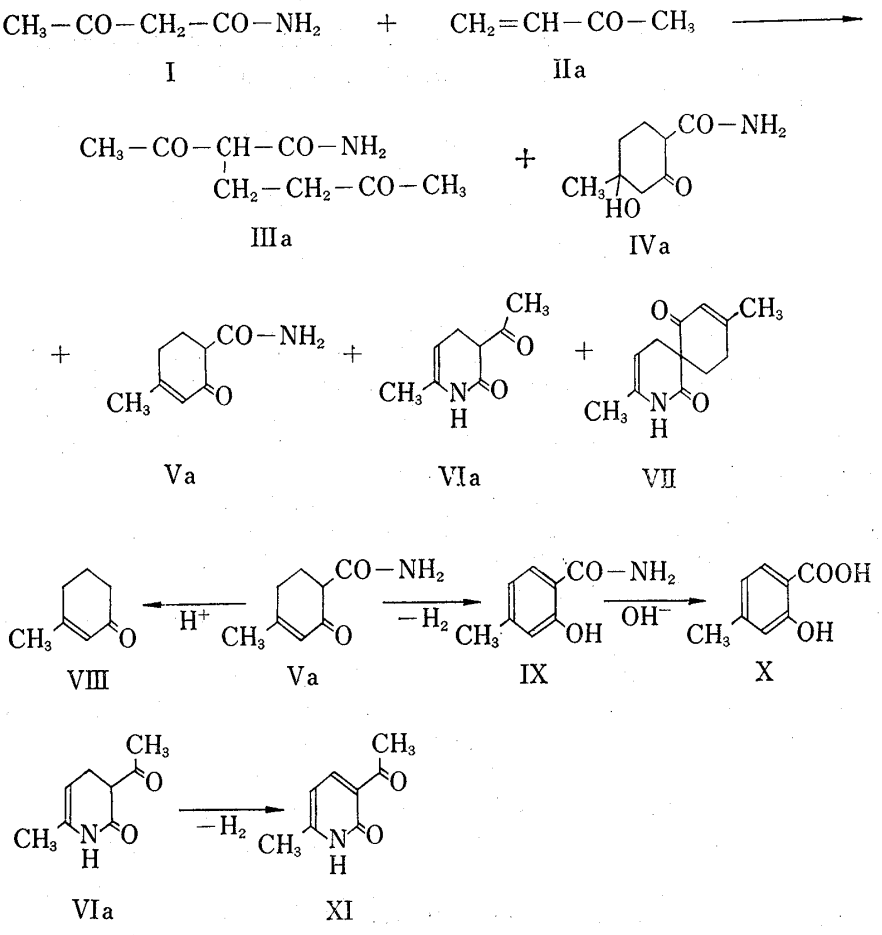

Chart 1

The probable mechanism of the formation of these products is shown in Chart 2. Michael addition of acetoacetamide (I) to 3-buten-2-one (IIa) gives rise to 3-carbamoyl-2,6-heptanedione (IIIa). Aldol addition between C_1-methyl and C_6-carbonyl of IIIa affords the carbocyclic isomer IVa along pathway-a. Cyclization between C_6-carbonyl and amide nitrogen of IIIa along pathway-b gives VIa *via* the heterocyclic intermediate XII.

Further Michael reaction of IIa with either Va or VIa affords an intermediate XIII or XIV, respectively subsequent cyclization of which gives rise to the spiro compound VII.

Similarly, reactions of acetoacetamide with 3-penten-2-one (IIb), 4-methyl-3-penten-2-one (IIc), 4-phenyl-3-buten-2-one (IId), and 2-benzylideneacetophenone (IIe) were tried. In these cases reaction conditions influenced the product formed. For instance, reactions in

5) P. Robe and E. Pollack, *Chem. Ber.*, **45**, 2924 (1912).
6) O. Jacobsen, *Chem. Ber.*, **16**, 1962 (1883).

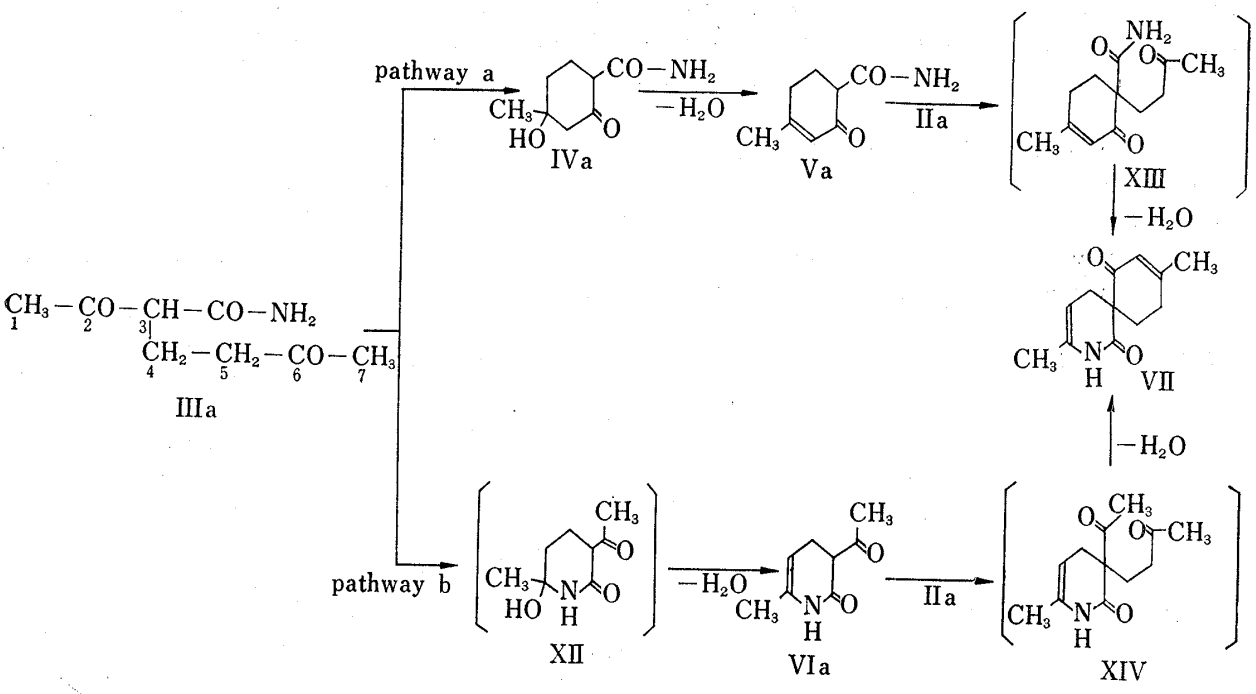

Chart 2

the presence of triethylamine resulted in the recovery of starting materials except IIe, which afforded a Michael adduct IIIe in 67% yield. Treatment of IIIe with sodium ethoxide afforded Ve.

When the reaction was carried out under reflux, cyclohexenone derivatives (Vb, d, e) and dihydropyridone derivatives (VIb, d, e) were obtained from the corresponding ketones (IIb, d, e). The reaction, in which sodium ethoxide used, afforded VIb—e.

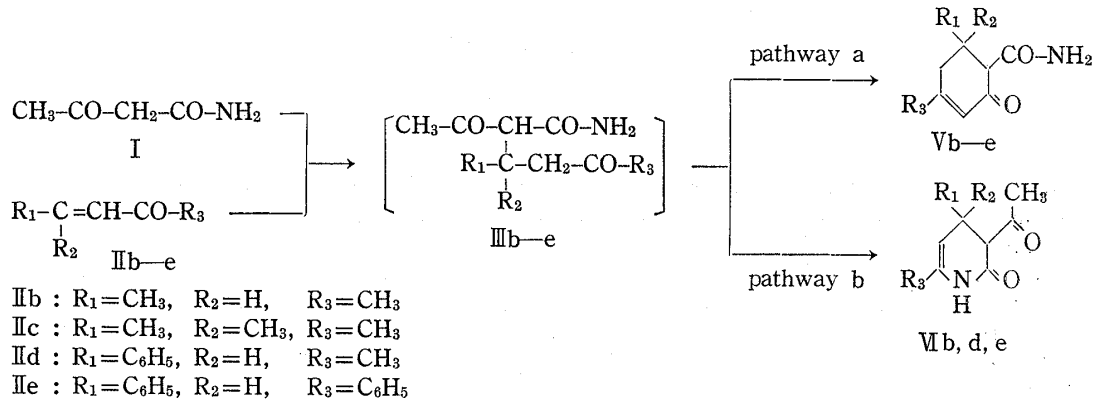

Chart 3

Reaction with α,β-Unsaturated Aldehydes

The similar reaction of I with α,β-unsaturated aldehyde such as crotonaldehyde (XVa) in the presence of triethylamine afforded a 1:1 adduct, $C_8H_{13}O_3N$ (XVIa) in 83% yield. Although three possible structures (XVIa′, XVIa″, and XVIa) corresponding to III, IV and XII could be given for the adduct, IR and NMR spectral data are consistent with the piperidone structure (XVIa), but not with the Michael adduct (XVIa′) or the cyclohexanone structure (XVIa″). For instance, in the NMR spectrum two signals due to CH_3 groups (singlet and doublet) are observed, but no signal due to aldehyde proton appears.

When the reaction was carried out in the presence of sodium ethoxide, 3-acetyl-4-methyl-3,4-dihydro-2(1H)-pyridone (XVIIa) and 3-acetyl-4-methyl-6-ethoxy-2-piperidone (XVIIIa)

were obtained in 59% and 3% yield, respectively. Disproportionation reaction of XVIIa with Pd-charcoal afforded 3-acetyl-4-methyl-2(1H)-pyridone (XIX) and 3-acetyl-4-methyl-2-piperidone (XX). Treatment of XIX with H_2SO_4 gave rise to 4-methyl-2(1H)-pyridone (XXI).[7]

Similarly, cinnamaldehyde (XVb) reacted with acetoacetamide (I) under the same condition giving XVIb, XVIIb and XVIIIb. The treatment of XVIa, b with sodium ethoxide gave rise to XVIIa, b and XVIIIa, b. XVIIa, b was also obtained by the treatment of XVIIIa, b with sodium ethoxide. Structural assignments of these products were made on the basis of elemental analysis, and spectral data.

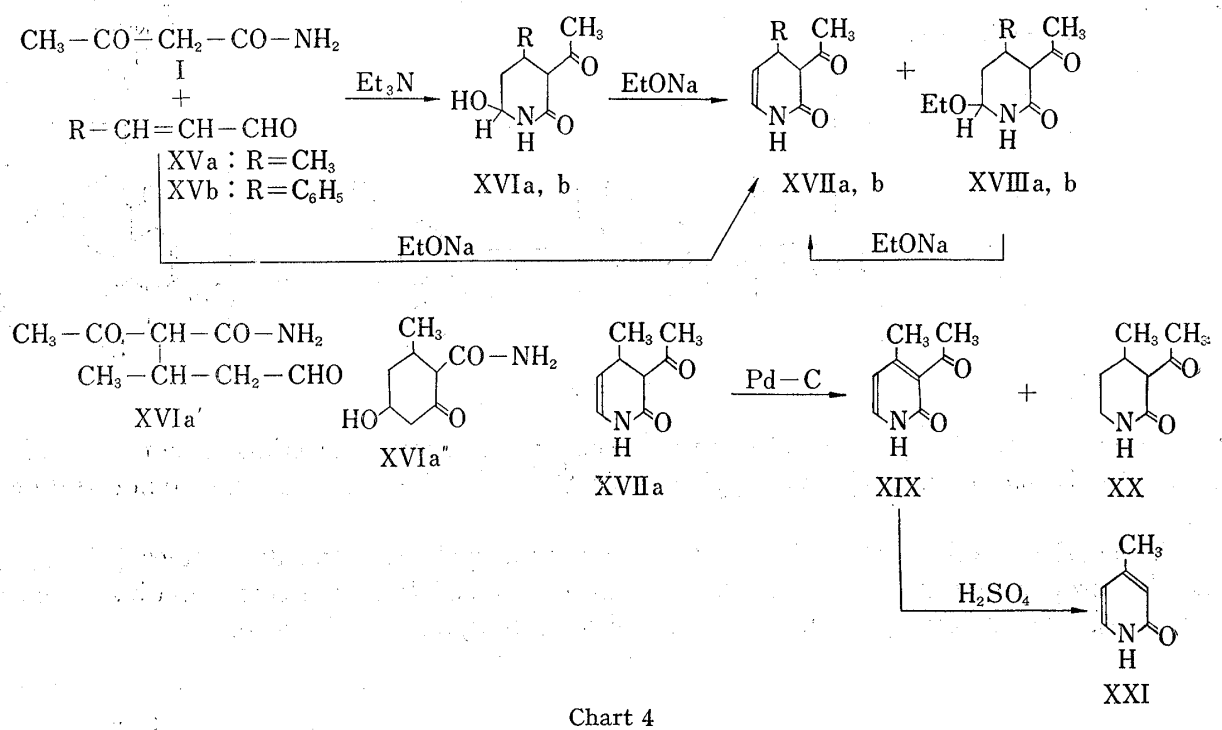

Chart 4

Experimental[8]

Reaction of Acetoacetamide (I) with 3-Buten-2-one (IIa)——1) To a solution of acetoacetamide (I) (3.5 g) and triethylamine (3 g) in abs. EtOH (50 ml), was added 3-buten-2-one (IIa) (2.1 g) dropwise. After stirring for 24 hr at room temperature, the reaction mixture was condensed *in vacuo*. The residue was washed with ether, and the resulting residual solid was purified by recrystallization from AcOEt to colorless needles (IIIa) of mp 117—118°. Yield, 2.96 g (57%). *Anal.* Calcd. for $C_8H_{13}O_3N$ (IIIa): C, 56.12; H, 7.65; N, 8.18. Found: C, 56.18; H, 7.70; N, 8.47. IR ν_{max}^{KBr} cm^{-1}: 1705, 1650. NMR ($CDCl_3$): 2.14 (3H, s, CH_3), 2.27 (3H, s, CH_3), 1.80—2.25 (2H, m, $-\underline{CH_2}-CH\langle$), 2.54 (2H, t, J=7.5 Hz, $CH_3-CO\underline{CH_2}-$), 3.41 (1H, t, J=7.5 Hz, $>\underline{CH}-$). 5.60—6.70 (2H, b, NH_2).

2) To a solution of I (3.5 g) and triethylamine (3 g) in abs. EtOH (50 ml), was added dropwise a solution of IIa (2.1 g) in abs. EtOH (15 ml) under reflux in a period of 30 min. The reaction mixture was refluxed for 24 hr. After removal of the solvent by vacuum distillation, the reaction mixture was purified by silica gel column chromatography using ether–petroleum ether and $CHCl_3$ as eluants. The ether–petroleum ether (1 : 4) fraction gave a crystalline substance, which was recrystallized from ether and petroleum ether to colorless prisms (VIa) of mp 105—106°. Yield, 0.3 g (6%). *Anal.* Calcd. for $C_8H_{11}O_2N$ (VIa): C, 62.72; H, 7.24; N, 9.14. Found: C, 62.57; H, 7.46; N, 9.31. IR ν_{max}^{KBr} cm^{-1}: 1700 (sh), 1650 (sh) 1620, 1610. NMR ($CDCl_3$): 1.78 (3H, m, CH_3), 1.88 (1.35 H, s, acetyl CH_3 (enol)), 2.30 (1.65H, s, acetyl CH_3 (keto)), 2.20—2.70 (1.1H, m, $-\underline{CH_2}-$),

7) R. Adams and A.W. Schrecker, *J. Am. Chem. Soc.*, **71**, 1186 (1949).

8) All melting points and boiling points were uncorrected. IR spectra were recorded on a Nippon-bunko Model IR-S spectrophotometer. NMR spectra were taken on a Hitachi-Perkin Elmer R-20 spectrometer at 60 MHz. Values are given in ppm relative to TMS as internal standard. Abbreviation are described as follows s=singlet, d=doublet, t=triplet, q=quartet, b=broad, sh=shoulder.

2.90—3.20 (0.9H, m, $-C\underline{H}_2-$), 3.42 (0.55H, t, $J=7.5$ Hz, $>C\underline{H}-$), 4.50—4.90 (1H, m, C_5–H), 7.18—8.30 (1H, b, NH), 14.07 (0.45H, s, enol OH).

The $CHCl_3$ eluted fraction gave a crystalline solid, which was recrystallized from AcOEt to colorless needles (Va) of mp 111—112°. Yield, 1 g (22%). *Anal.* Calcd. for $C_8H_{11}O_2N$ (Va): C, 62.72; H, 7.24; N, 9.14. Found: C, 62.77; H, 6.91; N, 9.04. IR ν_{max}^{KBr} cm^{-1}: 1685, 1660, 1625. NMR ($CDCl_3$): 1.96 (3H, s, CH_3), 2.10—2.50 (4H, m, $>C\underline{H}_2-\underline{C}\underline{H}_2\langle$), 5.86 (1H, b.s, C_2–H), 5.7—6.3 and 6.6—7.3 (2H, b, NH_2).

3) To a solution of I (3 g) in NaOEt–EtOH, prepared from Na (0.7 g) and abs. EtOH (50 ml), was added dropwise a solution of II (2.1 g) in abs. EtOH (15 ml) with stirring under ice-cooling over a period of 40 min. After stirring for 5 hr at 0°, the reaction mixture was neutralized with 10% HCl, and the solvent was removed by vacuum distillation. The residue was extracted with AcOEt. The AcOEt solution was condensed to give an oily substance, which was purified by silica gel column chromatography using ether–petroleum ether, $CHCl_3$ and AcOEt as eluants. From the ether–petroleum ether (1 : 4) fraction a crystalline substance was obtained. Recrystallization from ether–petroleum ether gave colorless prisms (VIa) of 105—106°. Yield, 0.4 g (8%). The $CHCl_3$ fraction gave colorless needles (VII) of mp 188—189° after recrystallization from ether. Yield, 0.35 g (5%). *Anal.* Calcd. for $C_{12}H_{15}O_2N$ (VII); C, 70.22; H, 7.35; N, 6.82. Found: C, 70.26; H, 7.27; N, 6.86. IR ν_{max}^{KBr} cm^{-1}: 1650, 1640, 1625. NMR ($CDCl_3$): 1.79 (3H, m, CH_3), 1.96 (3H, s, CH_3), 2.1—3.1 (6H, m, methylene), 4.70 (1H, m, C_4–H), 5.87 (1H, b.s, C_8–H), 7.3—7.7 (1H, b, NH). The AcOEt fraction gave crude crystalline solid, which was recrystallized from AcOEt to colorless needles (IVa) of mp 164—165°. Yield, 0.1 g (2%). *Anal.* Calcd. for $C_8H_{13}O_3N$ (IVa): C, 56.12; H, 7.65; N, 8.18. Found: C, 56.34; H, 7.10; N, 8.13. IR ν_{max}^{KBr} cm^{-1}: 1650, 1610. NMR ($CDCl_3$–CF_3COOH): 1.38 (3H, s, CH_3), 1.7—2.8 (6H, m, methylene), 3.2—3.6 (1H, m, $>C\underline{H}-$), 7.2—8.0 (2H, b, NH_2).

2-Carbamoyl-5-hydroxy-5-methylcyclohexanone (IVa)——To a NaOEt–EtOH solution, prepared from Na (80 mg) and abs. EtOH (20 ml), was added IIIa (0.6 g). After stirring for 5 hr at room temperature, the reaction mixture was neutralized with 10% HCl and condensed *in vacuo*. The resulting residue was extracted with AcOEt, and the AcOEt solution was dried, condensed to give a crystalline substance, which was purified by recrystallization from AcOEt to colorless needles (IVa) of mp 164—165°, undepressed on admixture with a sample obtained in the above run. Yield, 0.3 g (54%).

6-Carbamoyl-3-methyl-2-cyclohexenone (Va)——A solution of IVa (0.3 g) in conc. HCl (3 ml) was allowed to stand for 24 hr at room temperature. After neutralizing with $NaHCO_3$, the mixture was condensed to dryness, and the resulting residual solid was extracted with AcOEt. The AcOEt solution was dried, condensed to give a crystalline substance. Recrystallization from AcOEt afforded colorless needles (Va), undepressed on admixture with a specimen obtained in the above run. Yield, 0.15 g (56%).

3-Methyl-2-cyclohexenone (VIII)——A solution of Va (0.5 g) in conc. HCl (10 ml) was heated for 1 hr. The mixture was neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried, and condensed. The oily residue was purified by vacuum distillation to give a hydroscopic colorless oil of bp 87° (17 mmHg). Yield, 0.22 g (61%). *Anal.* Calcd. for $C_7H_{10}O \cdot 1/5H_2O$ (VIII): C, 73.91; H, 9.22: Found: C, 73.84; H, 9.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655, 1625. NMR ($CDCl_3$): 2.98 (3H, s, CH_3), 2.0—2.6 (6H, m, methylene), 5.86 (1H, b.s, C_2–H).

4-Methylsalycilamide (IX)——A mixture of Va (0.5 g) and 10% Pd–C (0.5 g) was heated at 200° for 10 min. After cooling, the mixture was extracted with MeOH. The MeOH solution was condensed, and the residue was purified by recrystallization from ether to colorless prisms of mp 176—177°. Yield, 0.17 g (34%). *Anal.* Calcd. for $C_8H_9O_2N$ (IX): C, 63.56; H, 6.00; N, 9.27. Found: C, 63.44; H, 6.20; N, 9.34. IR ν_{max}^{KBr} cm^{-1}: 1665, 1630, 1600. NMR ($CDCl_3$+CF_3COOH): 2.35 (3H, s, CH_3), 6.24 (1H, double d, C_5–H, $J=9$ Hz, $J=1.5$ Hz), 6.82 (1H, s, C_3–H), 7.34 (1H, d, C_6–H, $J=9$ Hz).

4-Methylsalicylic Acid (X)——A solution of IX (0.08 g) in 20% KOH (10 ml) was heated for 7 hr. The reaction mixture was acidified with conc. HCl. Crystals separated were collected, washed with H_2O, dried, and recrystallized from petroleum ether to colorless needles of mp 174—175° (lit.[6] mp. 174°). Yield, 0.03 g (37%). *Anal.* Calcd. for $C_8H_8O_3$ (X): C, 63.15; H, 5.30. Found: C, 62.96; H, 5.48. IR ν_{max}^{KBr} cm^{-1}: 1650, 1623. NMR ($CDCl_3$–CF_3COOH): 2.49 (3H, s, CH_3), 6.78 (1H, double d, C_5–H, $J=9$ Hz, $J=1.5$ Hz), 6.85 (1H, s, C_3–H), 7.81 (1H, d, C_6–H, $J=9$ Hz).

3-Acetyl-6-methyl-2(1H)-pyridone (XI)——A solution of VIa (0.14 g) and chloroanil (0.22 g) in benzene (20 ml) was refluxed for 2 hr. The reaction mixture was washed with a saturated $NaHCO_3$ solution. The $NaHCO_3$ soluble fraction was extracted with AcOEt. From the AcOEt soluble fraction, a crystalline substance was obtained, which was purified by recrystallization from AcOEt to give colorless needles (XI) of mp 201—202 (decomp.). From the benzene fraction a small amount of same crystals was obtained. Total yield, 68 mg (50%). *Anal.* Calcd. for $C_8H_9O_2N$ (XI): C, 63.56; H, 6.00; N, 9.27. Found: C, 62.99; H, 6.15; N, 9.30. IR ν_{max}^{KBr} cm^{-1}: 1660, 1615. NMR ($CDCl_3$–CF_3CO_2H): 2.52 (3H, s, CH_3), 2.67 (3H, s, CH_3), 6.59 (1H, d, C_5–H, 7.5 Hz), 8.37 (1H, d, C_4–H, $J=7.5$ Hz).

Reaction of I with 3-Penten-2-one (IIb)——1) To a NaOEt-EtOH solution, prepared from Na (0.7 g) and abs. EtOH (50 ml), were added I (3.5 g) and IIb (2.5 g) with stirring. After allowing to stand for 3 days, the mixture was neutralized with 10% HCl, and evaporated *in vacuo*. The residue was extracted with AcOEt. The AcOEt extract was purified by silica gel column chromatography using $CHCl_3$ as eluant to give a crystal-

line substance, which was recrystallized from ether to colorless needles of mp 143—144°. Yield, 1.2 g (24%). *Anal.* Calcd. for $C_9H_{13}O_2N$ (Vb): C, 64.65; H, 7.84; N, 8.38. Found: C, 64.30; H, 7.40; N, 8.20. IR ν_{max}^{KBr} cm^{-1}: 1660, 1635. NMR ($CDCl_3$): 1.07 (3H, d, CH_3, $J=6$ Hz), 1.94 (3H, s, CH_3), 2.0—3.1 (4H, m, methylene and methine), 5.87 (1H, b.s, C_2–H), 5.7—6.7 (2H, b, NH_2).

2) A solution of I (3.5 g), IIb (2.5 g) and triethylamine (6 g) in abs. EtOH (50 ml) was refluxed for 40 hr. After removal of the solvent, the oily residue was purified by silica gel chromatography. The ether–petroleum ether (1: 4) elution gave colorless needles of mp 88—89° (VIb). Yield, 0.14 g (2.8%). *Anal.* Calcd. for $C_9H_{13}O_2N$ (VIb): C, 64.65; H, 7.89; N, 8.38. Found: C, 64.62; H, 8.04; N, 8.36. IR ν_{max}^{KBr} cm^{-1}: 1715, 1695 (sh), 1665. NMR ($CDCl_3$): 1.05 (3H, d, CH_3, $J=6$ Hz), 1.79 (3H, d, CH_3, $J=0.78$ Hz), 2.25 (3H, s, acetyl CH_3), 2.5—3.2 (1H, m, >C<u>H</u>–CH_3), 3.18 (1H, d, >C<u>H</u>–$COCH_3$, $J=7.5$ Hz), 4.70 (1H, b.s, C_5–H), 7.8—8.3 (1H, b, NH).

The $CHCl_3$ elution afforded 1.2 g (24%) of Vb, mp 143—144°.

Reaction of I with 4-Methyl-3-penten-2-one (IIc)——To a solution of I (3.5 g) in NaOEt–EtOH, prepared from Na (0.7 g) and abs. EtOH (50 ml), was added 4-methyl-3-penten-2-one (IIc) (2.9 g). The mixture was allowed to stand at room temperature for 2 weeks. The reaction mixture was neutralized with 10% HCl, and the solvent was distilled off *in vacuo*. The residue was extracted with $CHCl_3$. The $CHCl_3$ solution was condensed to give an oily residue, which was purified by silica gel chromatography using ether and petroleum ether as eluants. After eluting with petroleum ether and then the mixture of petroleum ether and ether (1: 1), ether was then passed through the column, and from this fraction colorless prisms (Vc) of mp 142—143° were obtained. Yield, 1.3 g (24%). *Anal.* Calcd. for $C_{10}H_{15}O_2N$ (Vc): C, 66.27; H, 8.34; N, 7.73. Found: C, 65.88; H, 7.87; N, 7.63. IR ν_{max}^{KBr} cm^{-1}: 1685, 1665, 1638. NMR ($CDCl_3$): 1.06 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.99 (3H, s, CH_3), 1.8—2.2 (1H, m, –C<u>H</u>$_2$–), 2.8—3.1 (2H, m, –C<u>H</u>$_2$–, >C<u>H</u>–$CONH_2$), 5.90 (1H, b.s, C_2–H), 5.6—6.5 (2H, b, NH_2).

Reaction of I with 4-Phenyl-3-buten-2-one (IId)——1) To a solution of I (3.5 g) in NaOEt–EtOH, prepared from Na (0.7 g) and abs. EtOH (50 ml) was added 4-phenyl-3-buten-2-one (IId) (4.35 g). After allowing to stand at room temperature for 2 days, the reaction mixture was neutralized with 10% HCl, and the mixture was condensed *in vacuo*. The residue was extracted with AcOEt. The AcOEt solution was condensed, and crystals separated were collected. Recrystallization from AcOEt afforded colorless plates (Vd) of mp 134—135°. Yield, 3.6 g (52%). *Anal.* Calcd. for $C_{14}H_{15}O_2N$ (Vd): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.59; H, 6.52; N, 6.20. IR ν_{max}^{KBr} cm^{-1}: 1650, 1625. NMR ($CDCl_3$): 2.00 (3H, s, CH_3), 2.5—2.8 (2H, m, –C<u>H</u>$_2$–), 3.43 (1H, d, >C<u>H</u>–$CONH_2$, $J=9.75$ Hz), 3.6—4.1 (1H, m, >C<u>H</u>–C_6H_5), 5.1—6.3 (2H, b, NH_2), 6.00 (1H, b.s, C_2–H), 7.24 (5H, s, C_6H_5).

2) A solution of I (3.5 g), triethylamine (6 g) and IId (4.35 g) in abs. EtOH (50 ml) was refluxed for 40 hr. The solvent was removed by vacuum distillation, and the resulting oily residue was purified by silica gel chromatography using ether–petroleum ether, and $CHCl_3$ as eluants. The ether–petroleum ether (1: 1) fraction gave colorless needles (VId) of mp 138—139°. Yield, 0.45 g (6.5%). *Anal.* Calcd. for $C_{14}H_{15}O_2N$ (VId): C, 73.34; H, 6.59; N, 6.11. Found: 73.37; H, 6.82; N, 6.04. IR ν_{max}^{KBr} cm^{-1}: 1700 (sh), 1633, 1605. NMR ($CDCl_3$): 1.77 (6H, s, CH_3, acetyl CH_3 (enol)), 4.2—4.4 (1H, m, >C<u>H</u>–C_6H_5), 4.68—4.85 (1H, m, C_5–H), 7.25 (5H, s, C_6H_5), 7.4—7.7 (1H, b, NH), 14.72 (1H, s, enol OH). From the $CHCl_3$ elution colorless plates (Vd) of mp 134—135° were obtained. Yield, 2.0 g (29%).

Reaction of I with 2-Benzylideneacetophenone (IIe)——1) To a solution of I (3.5 g) and triethylamine (3 g) in abs. EtOH (50 ml), was added 2-benzylideneacetophenone (IIe) (6.1 g) with stirring. After several min, the reaction mixture was solidified, to which abs. EtOH (40 ml) was added and the mixture was stirred for 5 days at room temperature. The solvent was removed by vacuum distillation and the residual solid was purified by recrystallization from EtOH to colorless needles (IIIe) of mp 179—180°. Yield, 6.1 g (67%). *Anal.* Calcd. for $C_{19}H_{19}O_3N$ (IIId): C, 73.76; H, 6.19; N, 4.53. Found: C, 73.71; H, 6.36; N, 4.55. IR ν_{max}^{KBr} cm^{-1}: 1730, 1685, 1650. NMR (DMSO-d_6): 1.93 (3H, s, CH_3), 3.2—3.5 (2H, m, –C<u>H</u>$_2$–), 3.98 (1H, d, >C<u>H</u>–$COCH_3$, $J=3.0$ Hz), 3.85—4.15 (1H, m, >C<u>H</u>–), 7.15 (5H, s, C_6H_5), 7.2—8.0 (7H, m, C_6H_5, NH_2).

2) A solution of I (3.5 g), triethylamine (6 g) and 2-benzylideneacetophenone (6.1 g) in abs. EtOH (50 ml) was refluxed for 24 hr. The solvent was distilled off *in vacuo*, and the resulting crystalline residue was recrystallized from MeOH to colorless needles (Ve) of mp 177—178°. Yield, 7.5 g (86%). *Anal.* Calcd. for $C_{19}H_{17}O_2N$ (Ve): C, 78.33; H, 5.88; N, 4.81. Found: C, 78.63, H, 5.90; N, 4.82. IR ν_{max}^{KBr} cm^{-1}: 1650, 1600. NMR ($CDCl_3$): 2.9—3.3 (2H, m, –C<u>H</u>$_2$–), 3.56 (1H, d, >C<u>H</u>–$CONH_2$, $J=9$ Hz), 3.7—4.3 (1H, m, >C<u>H</u>–), 5.2—6.3 (1H, b, NH_2), 6.51 (1H, b.s, C_2–H), 7.23 (5H, s, C_6H_5), 7.40 (5H, b.s, C_6H_5).

The filtrate was condensed and the oily residue was purified by silica gel chromatography using ether–petroleum ether (1: 1) as eluants. From this fraction, colorless prisms (VIe) of mp 141—142° were obtained. Yield, 0.06 g (0.7%). *Anal.* Calcd. for $C_{19}H_{17}O_2N$ (VIe): C, 78.33; H, 5.88; N, 4.81. Found: C, 77.98; H, 6.14; N, 4.82, IR ν_{max}^{KBr} cm^{-1}: 1720 (sh), 1663, 1620. NMR ($CDCl_3$): 1.81 (2H, acetyl CH_3 (enol)), 2.23 (1H, acetyl CH_3 (keto)), 3.75 (1/3H, >C<u>H</u>–$COCH_3$), 4.1—4.5 (1H, m, >C<u>H</u>–C_6H_5), 5.2—5.6 (1H, m, C_5–H), 7.2—7.45 (10H, m, $C_6H_5\times2$), 7.2—8.2 (1H, b, NH), 14.66 (2/3H, s, enol OH).

3) To a solution of I (3.5 g) in NaOEt–EtOH, prepared from Na (0.7 g) and abs. EtOH (50 ml), was added 2-benzylideneacetophenone (IIe) (6.1 g). After allowing to stand at room temperature for 1 day, the reaction mixture was neutralized with 10% HCl, and the mixture was condensed *in vacuo*. The residue was treated

with H_2O. The crystals separated were collected and recrystallized from benzene to give colorless needles (Ve). Yield, 6.2 g (71%).

6-Carbamoyl-3,5-diphenyl-2-cyclohexenone (Ve)——A mixture of IIIe (1 g) and a NaOEt–EtOH solution, prepared from Na (80 mg) and abs. EtOH (20 ml), was stirred at room temperature for 2.5 hr. The mixture was neutralized with 10% HCl, and condensed *in vacuo*. The residue was extracted with AcOEt. The AcOEt solution was dried, condensed, and the resulting crystalline solid was recrystallized from AcOEt to colorless needles(Ve) of mp 177—178°, undepressed on admixture with a sample obtained in the above run. Yield, 0.67 g (70%).

Reaction of I with Crotonaldehyde (XVa)——1) A solution of I (3.5 g), XVa (2.1 g) and triethylamine (0.7 g) in abs. EtOH (50 ml) was stirred for 6 days at room temperature. Crystals precipitated were collected by suction. Yield, 1.2 g. The filtrate was evaporated to give a crystalline solid, which was recrystallized from AcOEt to 3 g of colorless needles. Total yield, 4.2 g (83%), mp 115—116°. *Anal.* Calcd. for $C_8H_{13}O_3N$ (XVIa): C, 56.12. H, 7.65; N, 8.18. Found: C, 56.41; H, 7.71; N, 8.08. IR ν_{max}^{KBr} cm^{-1}: 1705, 1640 (sh), 1605. NMR (DMSO-d_6): 0.94 (3H, d, CH_3, J=6.75 Hz), 2.23 (3H, s, CH_3), 1.3—2.1 (3H, m, >C<u>H</u>$_2$–C<u>H</u><), 2.98 (1H, double d, >C<u>H</u>–$COCH_3$, J=10.5 Hz, J=3.75 Hz), 3.8—4.5 (1H, b, OH), 4.92 (1H, double d, >C<u>H</u>–OH, J=6 Hz, J=3 Hz), 7.6—8.6 (1H, b, NH).

2) To a solution of I (3.5 g) in a NaOEt–EtOH solution, prepared from Na (0.2 g) and abs. EtOH (50 ml), was added dropwise a solution of XVa in abs. EtOH (10 ml) under ice-cooling in a period of 30 min. After stirring for 30 min, the reaction mixture was neutralized with 10% HCl and condensed under reduced pressure. The residue was extracted with $CHCl_3$. The $CHCl_3$ extract was purified by silica gel column chromatography. The ether–petroleum ether (1: 1) fraction gave a crystalline solid. Recrystallization from petroleum benzine afforded colorless needles (XVIIa) of mp 75—77°. Yield, 2.7 g (59%). *Anal.* Calcd. for $C_8H_{11}O_2N$ (XVIIa): C, 62.72; H, 7.24; N, 9.14. Found: C, 62.66; H, 7.04; N, 9.15. IR ν_{max}^{KBr} cm^{-1}: 1715, 1670, 1645, 1615. NMR ($CDCl_3$): 1.08 (3H, d, CH_3, J=6.75 Hz), 2.00 (1.23H, s, acetyl CH_3 (enol)), 2.29 (1.77H, s, acetyl CH_3 (keto)), 3.25 (0.59H, d, >C<u>H</u>–$COCH_3$, J=7.5 Hz), 2.8—3.3 (1H, m, >C<u>H</u>–CH_3), 5.02 (1H, double d, C_5–H, J=7.5 Hz, J=3 Hz), 5.95 (1H, double d, C_6–H, J=7.5 Hz, J=4.5 Hz), 7.2—8.4 (1H, b, NH), 14.3 (0.41H, s, enol OH).

The elution was continued with the same solvent giving colorless plates (ether) of mp 102—103°. Yield, 0.2 g (3%). *Anal.* Calcd. for $C_{10}H_{17}O_3N$ (XVIIIa): C, 60.28; H, 8.60; N, 7.03. Found: C, 59.84; H, 8.65; N, 6.81. IR ν_{max}^{KBr} cm^{-1}: 1715, 1660. NMR ($CDCl_3$): 0.98 (3H, d, CH_3, J=6.75 Hz), 2.21 (3H, t, –CH_2–<u>CH_3</u>, J=6.75 Hz), 2.26 (3H, s, CH_3), 2.26—2.1 (2H, m, –<u>CH_2</u>–), 2.4—2.9 (1H, m, >C<u>H</u>–CH_3), 2.99 (1H, d, >C<u>H</u>–$COCH_3$, J=10.5 Hz), 3.52 (2H, t, –<u>CH_2</u>–CH_3, J=6.75 Hz), 4.61 (1H, double d, >C<u>H</u>–OC_2H_5, J=6 Hz, J=3 Hz), 7.2—8.1 (1H, b, NH).

Reaction of I with Cinnamaldehyde (XVb)——1) To a solution of I (3.5 g) and triethylamine (0.7 g) in abs. EtOH (50 ml), was added dropwise cinnamaldehyde (XVb) (3.9 g) with stirring. Stirring was continued at room temperature for 2 days, to give a crystalline substance. Recrystallization from ether gave colorless needles (XVIb) of mp 157—158°. Yield, 3.3 g (43%). *Anal.* Calcd. for $C_{13}H_{15}O_3N$ (XVIb): C, 66.93; H, 6.48; N, 6.01. Found: C, 67.09; H, 6.54; N, 6.15. IR ν_{max}^{KBr} cm^{-1}: 1700, 1650, 1640. NMR (DMSO-d_6): 1.05 (3H, s, CH_3), 1.5—2.2 (2H, m, –<u>CH_2</u>–), 3.74 (1H, d, >C<u>H</u>–$COCH_3$, J=3.75 Hz), 3.6—3.9 (1H, m, >C<u>H</u>–C_6H_5), 3.8—4.4 (1H, b, OH), 4.94 (1H, double d, >C<u>H</u>–OH, J=6 Hz, J=3 Hz), 7.26 (5H, s, C_6H_5), 7.8—8.5 (1H, b, NH).

2) To a solution of (I) (3.5 g) in a NaOEt–EtOH solution, prepared from Na (0.2 g) and abs. EtOH (10 ml) was added dropwise a solution of XVb (3.9 g) in abs. EtOH (10 ml) with stirring under ice-cooling in a period of 30 min. After stirring for 1 hr at the same temperature, the mixture was neutralized with 10% HCl. The solvent was removed by vacuum distillation. A small amount of ether was added to the oily residue followed by rubbing with a glass rod. Crystals separated were collected. Recrystallization from benzene gave colorless needles of mp 144—146° (XVIIb). Mother liquor was purified by silica gel chromatography. The $CHCl_3$ fraction gave the same crystals of mp 144—146°. Total yield, 2.8 g (43%). *Anal.* Calcd. for $C_{13}H_{13}O_2N$ (XVIIb): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.67; H, 5.63; N, 6.37. IR ν_{max}^{KBr} cm^{-1}: 1610. NMR ($CDCl_3$): 1.78 (3H, s, acetyl CH_3 (enol)), 4.32 (1H, d, >C<u>H</u>–C_6H_5, J=5.25 Hz), 4.99 (1H, m, C_5-H), 5.90 (1H, m, C_6-H), 7.22 (5H, s, C_6H_5), 7.4—7.8 (1H, b, NH), 14.67 (1H, s, enol OH).

The elution was continued with $CHCl_3$, and a crystalline substance was subsequently obtained. Recrystallization from ether gave colorless prisms (XVIIIb) of mp 125—126°. Yield, 0.5 g (6%). *Anal.* Calcd. for $C_{15}H_{19}O_3N$ (XVIIIb): C, 68.94; H, 7.33; N, 5.36. Found: C, 69.09; H, 6.95; N, 5.33. IR ν_{max}^{KBr} cm^{-1}: 1715, 1655. NMR ($CDCl_3$): 1.22 (3H, t, –CH_2–<u>CH_3</u>, J=6.75 Hz), 2.11 (3H, s, acetyl CH_3), 1.9—2.3 (2H, m, –<u>CH_2</u>–), 3.52 (2H, q, –<u>CH_2</u>–CH_3, J=6.75 Hz), 3.70 (1H, d, >C<u>H</u>–$COCH_3$, J=4.5 Hz), 3.6—3.9 (1H, m, >C<u>H</u>–C_6H_5), 4.63 (1H, double d, >C<u>H</u>–OC_2H_5, J=6 Hz, 3 Hz), 7.29 (5H, s, C_6H_5), 7.2—8.0 (1H, b, NH).

Disproportionation Reaction of 3-Acetyl-4-methyl-3,4-dihydro-2(1H)-pyridone (XVIIa)——A mixture of XVIIa (0.5 g) and 10% Pd–C (0.5 g) was heated at 200° for 7 min. After cooling, the reaction mixture was extracted with MeOH. The MeOH layer was condensed, and the residue was crystallized from ether to colorless plates of mp 169—170° (XIX). Yield, 0.15 g (29%). *Anal.* Calcd. for $C_8H_9O_2N$ (XIX): C, 63.56; H, 6.00; N, 9.27. Found: C, 63.92; H, 6.16; N, 9.28. IR ν_{max}^{KBr} cm^{-1}: 1685, 1635, 1610, 1525. NMR ($CDCl_3$):

2.25 (3H, s, CH_3), 2.58 (3H, s, acetyl CH_3), 6.15 (1H, d, C_5-H, J=6 Hz), 7.29 (1H, d, C_6-H, J=6 Hz), 12.8—13.4 (1H, b, NH).

The filtrate was condensed and the residue was recrystallized from ether–petroleum ether to colorless prisms (XX) of mp 94—95°. Yield, 0.13 g (25%). *Anal.* Calcd. for $C_8H_{13}O_2N \cdot 1/10H_2O$ (XX): C, 61.21; H, 8.48; N, 8.92. Found: C, 61.30; H, 7.93; N, 9.27. IR ν_{max}^{KBr} cm^{-1}: 1715, 1650. NMR ($CDCl_3$): 1.02 (3H, d, CH_3, J=6.5 Hz), 2.33 (3H, s, acetyl CH_3), 1.4—2.2 (3H, m, $-C\underline{H}_2-C\underline{H}\langle^{CH_3)}$, 3.1—3.5 (3H, m, $-C\underline{H}_2-NH-$, $\rangle C\underline{H}-COCH_3$), 6.9—7.4 (1H, b, NH).

4-Methyl-2(1H)-pyridone (XXI)——A solution of XIX (0.1 g) in 70% H_2SO_4 (4 ml) was heated at 150° for 10 min. The reaction mixture was neutralized with $NaHCO_3$ and condensed to dryness. The residue was extracted with MeOH. The extract was condensed to give a crystalline substance. Recrystallization from ether afforded colorless prisms of mp 126—127° (XXI) (lit.[7] mp 130°). Yield, 0.04 g (55%). *Anal.* Calcd. for C_6H_7ON (XXI): C, 66.03; H, 6.47; N, 12.84. Found: C, 65.86; H, 6.43; N, 12.66. IR ν_{max}^{KBr} cm^{-1}: 1645, 1610, 1530. NMR ($CDCl_3$): 2.21 (3H, s, CH_3), 6.09 (1H, double d, C_5–H, J=6 Hz, J=1.5 Hz), 6.35 (1H, b.s, C_3–H), 7.26 (1H, d, C_6–H, J=6 Hz).

Reaction of 3-Acetyl-6-hydroxy-4-methyl-2-piperidone(XVIa) with NaOEt——A solution of XVIa (0.5 g) in NaOEt–EtOH, prepared from Na (23 mg) and EtOH (10 ml), was stirred for 20 min at 0°. After neutralization with 10% HCl, the solvent was distilled off *in vacuo*. The residue was extracted with $CHCl_3$. The $CHCl_3$ extract was purified by silica gel column chromatography. From the ether–petroleum ether (1: 1) fraction colorless needles (XVIIa) of mp 75—77° were obtained. Yield, 0.1 g (22%). The ether fraction gave colorless prisms (XVIIIa) of mp 102—103°. Yield, 0.15 g (26%).

Reaction of 3-Acetyl-6-hydroxy-4-phenyl-2-piperidone (XVIb) with NaOEt——Following the similar procedure as above, the reaction of XVIb (0.7 g) with NaOEt in EtOH gave 0.1 g (13%) of XVIIb and 0.2 g (26%) of XVIIIb.

Reaction of 3-Acetyl-6-ethoxy-4-methyl-2-piperidone (XVIIIa) with NaOEt——A mixture of XVIIIa (0.3 g) in a NaOEt–EtOH solution, prepared from Na (10 mg) and EtOH (6 ml), was stirred for 1 hr at room temperature. The reaction mixture was neutralized with 10% HCl and condensed *in vacuo*. The residue was submitted to silica gel chromatography using a mixture of ether–petroleum ether (1: 1) as eluant, from which a small amount (13 mg, 5.7%) of XVIIa was obtained.

Reaction of 3-Acetyl-6-ethoxy-4-phenyl-2-piperidone (XVIIIb) with NaOEt——Employing the similar procedure as above, reaction of XVIIIb (0.26 g) with NaOEt gave 10 mg (4.7%) of XVIIb.

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