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Studies on Ketene and Its Derivatives. XLI.[1] Reaction of α-Aminoketone with Diketene

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The reaction of diketene with α-aminoketone derivatives was studied. Ethyl α-aminoacetoacetate (IIIa) and 3-aminoacetylacetone (IIIb) react with diketene to give 3-acetyl-5-carbethoxy-2-hydroxypyrrole (IVa) and 3,5-diacetyl-2-hydroxy-4-methylpyrrole (IVb), respectively. α-Aminoacetone (IIIc) and phenacylamine (IIId) afford N-acetonylacetoacetamide (Ic) and N-phenacylacetoacetamide (Id). On treatment with dilute alkali, Ic and Id are transformed to 3-acetyl-4-methyl-3-pyrrolin-2-one (IVc) and 3-acetyl-4-phenyl-3-pyrrolin-2-one (IVd), respectively.

It is reported that[3,4] ethyl α-aminoester reacts with diketene to give α-acetoacetamino derivative (I), which, in the presence of sodium ethoxide, cyclizes to 3-acetyltetramic acid (II). On the other hand, we have previously shown that upon catalytic reduction with palladium-charcoal in ethanolic hydrochloric acid ethyl α-hydroximinoacetoacetate was reduced to ethyl α-aminoacetoacetate (IIIa) in almost quantitative yield.[5] While investigating of some potential uses of diketene, it occurred to us that reaction of IIIa with diketene might afford 3,5-diacetyltetramic acid (II where R=$COCH_3$). However, as shown in Chart 1 we have found that the reaction does not afford the tetramic acid derivative (II, R=$COCH_3$), but cyclization took place by dehydration giving 3-acetyl-5-carbethoxy-2-hydroxy-4-methylpyrrole (IVa). Going a step further, we investigated reaction of α-aminoketone derivatives (III) with diketene, which is the subject of the present paper.

In addition, during the course of this investigation we have found a facile route of synthesis of α-aminoacetone (IIIc), which is also described in this report.

When ethyl α-aminoacetoacetate hydrochloride (IIIa-HCl) was allowed to react with excess-diketene in the presence of sodium acetate, yellow scaly crystals of mp 167—168°, $C_{10}H_{13}O_4N$ (IVa), and colorless prisms of 2,5-dimethyl-3,6-dicarbethoxypyrazine (Va), mp 85°,[6] were obtained, but none of the product corresponding to the compound II (where R is acetyl) was detected. The former compound was identified with 3-acetyl-5-carbethoxy-2-hydroxy-4-methylpyrrole (IVa). The infrared (IR) spectrum of IVa in chloroform indicates the presence of the ester and acetyl carbonyl at 1681 and 1629 cm^{-1}, the C=C streching of pyrrole ring at 1575 cm^{-1}, and NH at 3472 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum of IVa in chloroform-d shows two singlets due to 4-methyl and 3-acetylmethyl protons at 2.42 ppm (3H) and 2.52 ppm (3H), a triplet (1.35 ppm, 3H) and a quartet (4.3 ppm, 2H) owing to the ethoxy protons, two broad signals of NH (8.85 ppm, 1H) and OH (*ca.* 12 ppm, 1H). Although the keto-enol tautomerism might be possible, the above spectral data are consistent with the hydroxypyrrole structure (IVa) in a chloroform solution.

Heating of IVa with acetic anhydride gave the monoacetyl derivative (VIa), whose IR spectrum shows the presence of enolacetate at 1790 cm^{-1} and C=C streching of pyrrole ring

1) Part XL: T. Kato, Y. Yamamoto, and T. Sakamoto, *Yakugaku Zasshi*, **90**, 1400 (1970).
2) Location: *a) Aobayama, Sendai; b) Kita-4, Sendai.*
3) R. Lacey, *J. Chem. Soc.*, **1954**, 850.
4) T. Kato and Y. Kubota, *Yakugaku Zasshi*, **87**, 1219 (1967).
5) T. Kato and M. Sato, *Yakugaku Zasshi*, **87**, 1209 (1967).
6) S. Gabriel and Th. Posner, *Ber.* **27**, 1141 (1894).

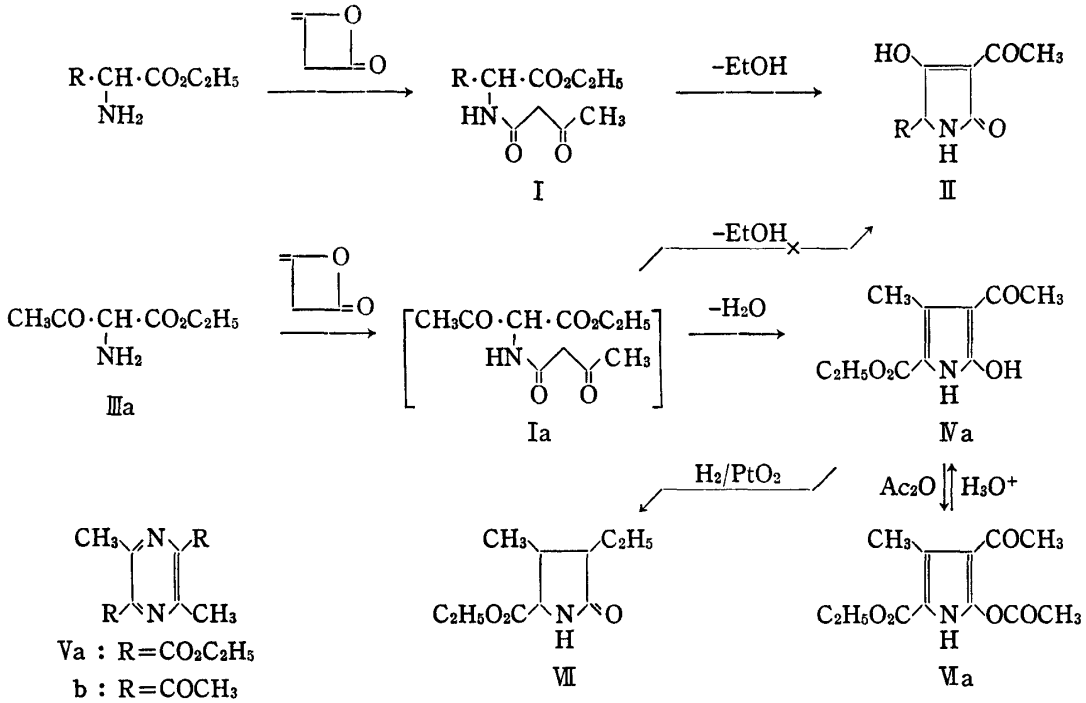

Chart 1

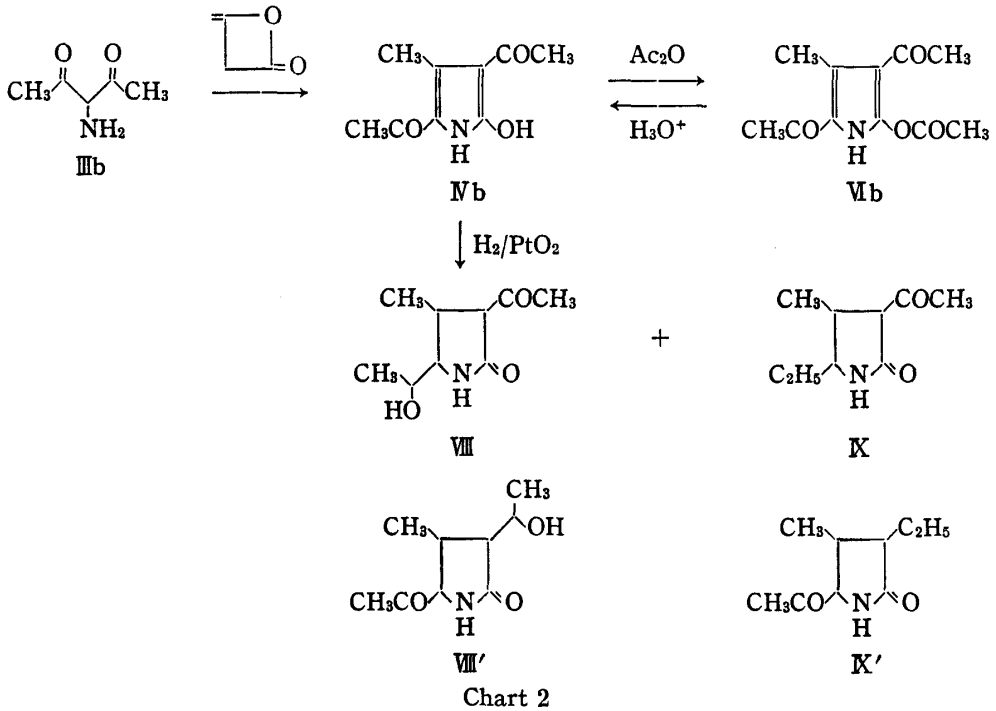

Chart 2

at 1575 cm^{-1}. Hydrolysis of VIa with dilute acid gave IVa *in situ*. Upon catalytic reduction with platinum oxide IVa was reduced to 5-carbethoxy-3-ethyl-4-methylpyrrolidin-2-one (VII).

Similarly, 3-aminoacetylacetone (IIIb)[7] reacted with diketene to yield 3,5-diacetyl-hydroxy-4-methylpyrrole (IVb) and 2,5-diacetyl-3,6-dimethylpyrazine (Vb, R=$COCH_3$).[7] Treatment of IVb with acetic anhydride afforded the monoacetyl derivative (VIb), which was readily hydrolyzed with dilute acid to give IVb.

7) V. Grinsteins and A. Veveris, *Latvijas PSR Zinatnu Akad. Vestis. Kim. Ser.*, **1962**, 463 (*Chem. Abstr.*, **59**, 12784 (1963)).

Catalytic reduction of IVb with platinum oxide gave two products, $C_9H_{15}O_3N$ (VIII) and $C_9H_{15}O_2N$ (IX), which gave both positive ferric chloride color test for the enol structure. This fact suggests that the 1,3-diketone structure (VIII and IX) will be considered as more plausible than the 5-acetyl structure of the isomers (VIII′ and IX′).

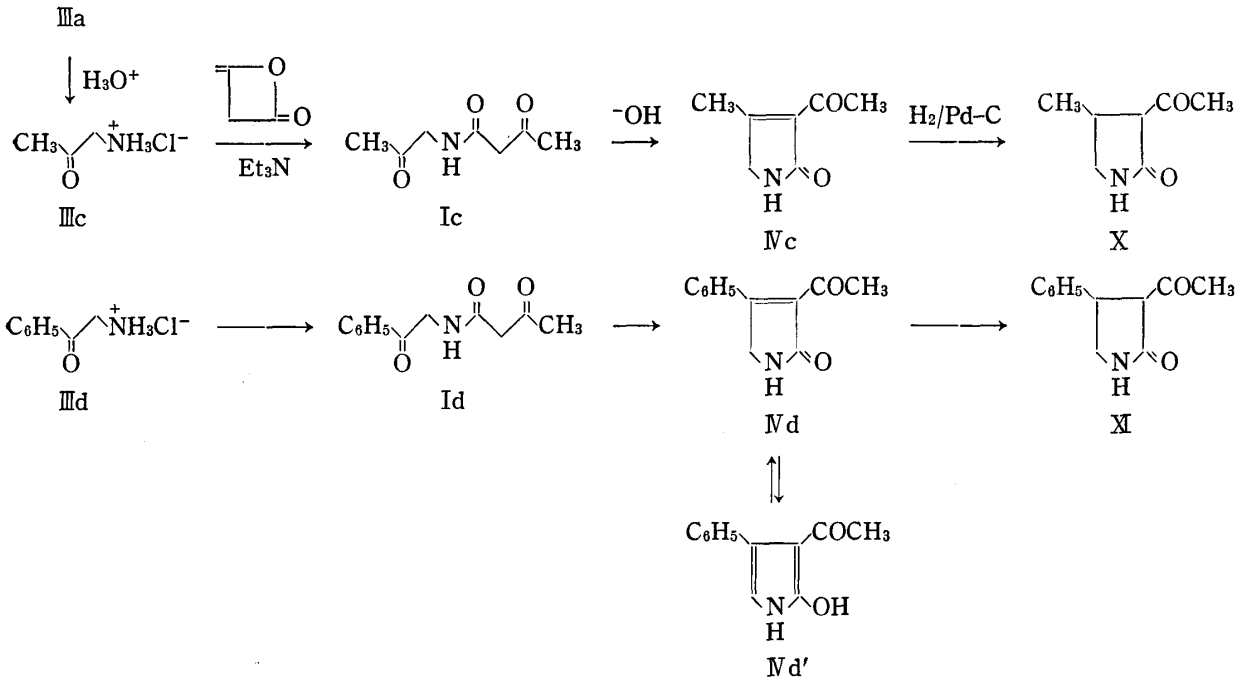

Chart 3

As an interesting sidelight of this investigation, we have found a facile preparative route to α-aminoacetone (IIIc); that is, when IIIa was heated at reflux in 20% hydrochloric acid, aminoacetone hydrochloride (IIIc-HCl) was obtained in almost quantitative yield. Since IIIa can be easily prepared,[5] this preparative route to IIIc will be worthy of note.

Following the same procedure given for IIIa, the reaction of IIIc with diketene in ethanol in the presence of sodium acetate resulted in the formation of a resinous product. However, when the reaction was carried out in ether in the presence of triethylamine, N-acetonylacetoacetamide (Ic) was obtained. Treatment of Ic with 10% sodium hydroxide afforded colorless needles, $C_7H_9O_2N$ (IVc), whose IR spectrum shows the presence of methyl ketone (1707 cm^{-1}), amide carbonyl (1690 cm^{-1}), and NH (3472, 3322 cm^{-1}). The NMR spectrum indicates three singlets due to 4-methyl (2.38 ppm), acetyl methyl (2.55 ppm), 5-methylene (4.0 ppm), and broad signal due to NH proton (7.75 ppm). These spectral data are consistent with the structure of 3-acetyl-4-methyl-3-pyrrolin-2-one (IVc).

Similarly, reaction of α-aminoacetophenone (IIId)[8] with diketene gave N-phenacylacetoacetamide (Id), which, on treatment with sodium hydroxide, was transformed to the pyrrolinone derivative (IVd).

It is of interest to see that the structure of IVc in chloroform exsists almost in the keto form but that of IVd exsists rather in the enol form (IVd′) than the keto form (IVd). Namely, the NMR spectrum clearly indicated that the tautomers IVd′ and IVd were presented in a 7:3 ratio.

Catalytic reduction of IVc and IVd with palladium–charcoal gave the dihydro derivatives, 3-acetyl-4-methylpyrrolidin-2-one (X) and 3-acetyl-4-phenylpyrrolidin-2-one (XI), respectively.

8) C. Mannich and F. Hahn, *Ber*, **44**, 1542 (1911).

Although there should be some stereo isomers in the case of the reduced products (VII—XI), we have not done experiments to identify these isomers.

Experimental

3-Acetyl-5-carbethoxy-2-hydroxy-4-methylpyrrole (IVa)——To a solution of ethyl α-aminoacetoacetate-HCl (IIIa-HCl) (3.6 g) and diketene (5 g) in 80% EtOH (30 ml), was added a solution of AcONa (3.3 g) in 5 ml of H_2O with stirring under ice-cooling. After stirring for 1 hr at room temperature, the mixture was condensed to dryness *in vacuo*. The residue was extracted with petroleum (petr.) benzine (bp 50—60°). From the petr. benzine soluble fraction colorless prisms, mp 85°, were obtained, undepressed on admixture with an authentic specimen of Va prepared according to the literature.[6] Yield, 0.15 g (7%). After washing with H_2O, the residual solid was purified by recrystallization from EtOH to yellow scaly crystals, mp 167—168°. Yield, 3.7 g (88%). *Anal.* Calcd. for $C_{10}H_{13}O_4N$ (IVa): C, 56.86; H, 6.20; N, 6.63. Found: C, 56.67; H, 6.26; N, 6.86.

3,5-Diacetyl-2-hydroxy-4-methylpyrrole (IVb)——Following to the procedure given for the above run, the mixture of 3-aminoacetylacetone-HCl (IIIb)[7] (1.5 g), diketene (2.5 g) in 80% EtOH (20 ml) was treated with AcONa (1.7 g). After stirring for 2 hr, the mixture was evaporated to dryness *in vacuo*. The residue was washed with petr. benzine (bp 50—60°), and then with H_2O. The resulting residue was purified by recrystallization from AcOEt to yellow needles, mp 189—191.5°. *Anal.* Calcd. for $C_9H_{11}O_3N$ (IVb): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.77; H, 6.23; N, 7.84. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3448 (NH), 1639, 1626 (CO). NMR $CDCl_3$, ppm: 2.43 (6H, s, 3 and 5-CH_3CO), 2.50 (3H, s, 4-CH_3), 9.2 (1H, b, NH), *ca.* 13 (1H, b, OH). The petr. benzine washing was condensed to give a crystalline solid, which was purified by recrystallization from petr. ether to yellow needles, mp 99—100°, undepressed on admixture with an authentic sample of Vb.[7]

2-Acetoxy-3-acetyl-5-carbethoxy-4-methylpyrrole (VIa)——A mixture of IVa (1 g) and Ac_2O (10 ml) was refluxed for 15 min. After removal of Ac_2O by vacuum distillation, the resulting residue was purified by recrystallization from petr. benzine to colorless needles, mp 121°. Yield, 0.8 g (67%). *Anal.* Calcd. for $C_{12}H_{15}O_5N$ (VIa): C, 56.91; H, 5.97; N, 5.53. Found: C, 57.28; H, 6.05; N, 5.58. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470, 3270 (NH), 1790, 1724, 1661 (CO), 1575 (C=C). NMR $CDCl_3$, ppm: 1.37 (3H, t, OCH_2CH_3), 2.40 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.60 (3H, s, CH_3), 4.34 (2H, q, OCH_2CH_3), 9.9 (1H, b, NH). A mixture of VIa (0.2 g) and 10% HCl (10 ml) was heated on a water bath for 5 min. After cooling, yellow crystals separated were collected by filtration. Recrystallization from EtOH gave yellow leaves of IVa, mp 167°. Yield, 0.14 g (85%).

5-Carbethoxy-3-ethyl-4-methylpyrrolidin-2-one (VII)——A mixture of IVa (0.2 g) and PtO_2 (0.1 g) in EtOH (30 ml) was shaken in H_2 with heating (*ca.* 50°) until *ca.* 50 ml of H_2 had been absorbed. The time required was about 10 hr. The catalyst was removed by filtration and the filtrate was condensed to give a crystalline solid, which was recrystallized from ether to give colorless needles, mp 114—114.5°. Yield, 50 mg (25%). *Anal.* Calcd. for $C_{10}H_{17}O_3N$ (VII): C, 60.28; H, 8.60; N, 7.03. Found: C, 60.13; H, 8.61; N, 7.10. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1739, 1709 (CO). NMR ($CDCl_3$, ppm): 1.30 (3H, t, OCH_2CH_3), 4.25 (2H, q, OCH_2-CH_3), 0.73 (3H, d, 4-CH_3), 4.24 (1H, d, 5-H), 2.85 (1H, q, 3-H), 2.5—0.8 (6H, m, 4-H and 3-C_2H_5), 6.4 (1H, b, NH).

2-Acetoxy-3,5-diacetyl-4-methylpyrrole (VIb)——A solution of IVb (0.18 g) in Ac_2O (2 ml) was heated at reflux for 30 min. After removal of Ac_2O by evaporation, the residue was recrystallized from benzene to colorless needles, mp 165—166°. Yield, 0.19 g (85%). *Anal.* Calcd. for $C_{11}H_{13}O_4N$ (VIb): C, 59.18; H, 5.87; N, 6.28. Found: C, 59.00; H, 5.95; N, 6.24. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3436, 3257 (NH), 1790, 1658 (CO), 1558 (C=C). NMR $CDCl_3$, ppm: 2.37 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.45 (3H, s, CH_3), 2.59 (3H, s, CH_3), 10.3 (1H, b, NH).

3-Acetyl-5- (1-hydroxyethyl)-4-methylpyrrolidin-2-one (VIII) and 3-Acetyl-5-ethyl-4-methylpyrrolidin-2-one (IX)——A mixture of IVb (0.36 g) and PtO_2 (0.1 g) in EtOH (40 ml) was shaken in H_2 until 40 ml of H_2 had been absorbed. The time required was about 2 hr. The catalyst was filtered off and the filtrate was condensed to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ and submitted to chromatography on silica gel. Elution with *n*-hexane–ether (1:1) gave colorless needles (*n*-hexane–ether), mp 102—103.5°. Yield, 55 mg (16%). *Anal.* Calcd. for $C_9H_{15}O_2N$ (IX): C, 63.88; H, 8.94; N, 8.26. Found: C, 63.86; H, 8.91; N, 8.30. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 3205 (NH), 1718, 1689 (CO). Subsequent elution with ether gave colorless needles (AcOEt), mp 165—166°. Yield, 56 mg (15%). *Anal.* Calcd. for $C_9H_{15}O_3N$ (VIII): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.34; H, 8.17; N, 7.56. IR ν_{max}^{KBr} cm^{-1}: 3510 (OH), 3215 (NH), 1724, 1689 (CO).

α-Aminoacetone Hydrochloride (IIIc-HCl)——IIIa-HCl (18 g)[5] was dissolved in 20% HCl (200 ml), and heated gently at reflux for 1 hr, during which time *ca.* 1 g of Norit was added. The reaction mixture was filtered and the filtrate was condensed *in vacuo* at 60—70° to give a syrupy residue, which was dried in a vacuum desiccator over P_2O_5 to form a crystalline solid, mp 75—78°. Recrystallization from absolute EtOH–ether gave colorless prisms, mp 81—82° (lit. mp 75°,[9] 81°[10]). Yield, 10.5 g (97%).

9) S. Gabriel and G. Pinkus, *Ber*, **35**, 3808 (1902).
10) A. Albert and S. Matsuura, *J. Chem. Soc.*, **1961**, 5131.

N-Acetonylacetoacetamide (Ic)——To a mixture of Ic-HCl (2.1 g), diketene (1.7 g) in dry ether (20 ml), was added dropwise a solution of Et_3N (2 g) in ether (5 ml) with ice-cooling. After stirring for 3 hr, the mixture was allowed to stand overnight at room temperature. The ether-insoluble precipitate was collected by suction, washed with dry ether and then extracted with hot benzene. The benzene soluble fraction was condensed to dryness *in vacuo*. The residue was purified by recrystallization from AcOEt to colorless prisms, mp 98—101°. Yield, 0.8 g (39%). *Anal.* Calcd. for $C_7H_{11}O_3N$ (Ic): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.71; H, 7.07; N, 8.63. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390, 3356 (NH), 1730, 1718, 1667 (CO). NMR $CDCl_3$, ppm: 2.20 (3H, s, CH_3), 2.28 (3H, s, CH_3), 3.47 (2H, s, $COCH_2CO$), 4.16 (2H, d, $NHCH_2$), 7.14 (1H, b, NH).

N-Phenacylacetoacetamide (Id)——Following the similar fashion described above, the mixture of IId-HCl[8] (8.64 g) and diketene (3.36 g) in ether (50 ml) was treated with a solution of Et_3N (4 g) in ether (10 ml) to give colorless leaves (benzene-ether), mp 86—87°. Yield, 7.4 g (84%). *Anal.* Calcd. for $C_{13}H_{13}O_3N$ (Id): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.71; H, 5.97; N, 6.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390 (NH), 1715, 1695, 1661 (CO). NMR $CDCl_3$, ppm: 2.27 (3H, s, CH_3), 3.48 (2H, s, $COCH_2CO$), 4.74 (2H, d, $NHCH_2$), 7.4—8.0 (6H, m, benzene ring protons and NH).

3-Acetyl-4-methyl-3-pyrrolin-2-one (IVc)——Ic (1.57 g) was added to 5 ml of 10% NaOH. After stirring for 5 min at room temperature, the mixture was neutralized with 10% HCl with ice-cooling, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4, filtered, and the solvent was removed from the filtrate by distillation. The residue was recrystallized from AcOEt to give colorless needles, mp 123—125° (decomp.). Yield, 0.93 g (67%). *Anal.* Calcd. for $C_7H_9O_2N$ (IV_C): C, 60.42; H, 6.52; N, 10.03. Found: C, 60.67; H, 6.40; N, 10.25.

3-Acetyl-4-phenyl-3-pyrrolin-2-one (IVd)——A solution of Id (4.4 g) in 10% NaOH (30 ml) was allowed to stand for 10 min and neutralized with 10% HCl at ice-cooling temperature. Crystals precipitated were collected by suction, washed with H_2O, and dried in a vacuum desiccator. Recrystallization from petr. benzine (bp 60—70°) afforded pale yellow scaly crystals, mp 119—121°. Yield, 3.6 g (90%). *Anal.* Calcd. for $C_{12}H_{11}O_2N$ (IVd): C, 71.62; H, 5.51; N, 6.96. Found: C, 71.88; H, 5.49; N, 6.78. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 3155 (NH, OH), 1709 (shoulder), 1686, 1648 (CO). NMR $CDCl_3$, ppm: 1.95 (2.1H, s, CH_3 of IVd'), 2.47 (0.9H, s, CH_3 of IVd), 4.35 (0.6H, s, 5-CH_2 of IVd), 6.2 (0.7H, s, 5-H of IVd'), 7.9 (0.3H, b, NH of IVd), 9.1 (0.7H, b, NH of IVd'), 11.5 (0.7H, b, 2-OH of IVd').

3-Acetyl-4-methylpyrrolidin-2-one (X)——A mixture of IVc (0.7 g) and 5% Pd-C (0.3 g) in MeOH (20 ml) was shaken in H_2. After 30 min, 110 ml of H_2 was absorbed. The catalyst was removed by filtration, and the solvent was evaporated from the filtrate. The residue was chromatographed on silica gel. Elution with ether afforded colorless needles (petr. benzine-ether), mp 55—58°. Yield, 0.4 g (57%). *Anal.* Calcd. for $C_7H_{11}O_2N$ (X): C, 59.55; H, 7.85; N, 9.92. Found: C, 59.50; H, 7.89; N, 9.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370, 3170 (NH), 1693 (CO). NMR $CDCl_3$, ppm: 1.1 (3H, m, 4-CH_3), 2.30 (3H, s, $COCH_3$), 2.7—3.1 (3H, m, 4-H, 5-CH_2), 3.3—3.6 (1H, m, 3-H).

3-Acetyl-4-phenylpyrrolidin-2-one (XI)——The mixture of IVd (1 g) and 5% Pd-C (0.3 g) in MeOH (15 ml) was shaken in H_2 until 120 ml of H_2 had been absorbed. The time required was *ca.* 2 hr. The catalyst was filtered off and the solvent was evaporated. The residue was recrystallized from ether to give colorless prisms, mp 135—136°. Yield, 0.72 g (72%). *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.01, H, 6.59; N, 6.65. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3200 (NH), 1710, 1695 (CO). NMR ($CDCl_3$, ppm): 2.36 (3H, s, $COCH_3$), 3.2—4.35 (4H, m, pyrrolidine ring protons), 7.0 (1H, b, NH), 7.2 (5H, s, phenyl).

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