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Studies on O-Alkylated Imides. II.[1] Some Reactions of O-Ethyl Succinimide and O-Ethyl 4,4-Dimethyl-glutarimide

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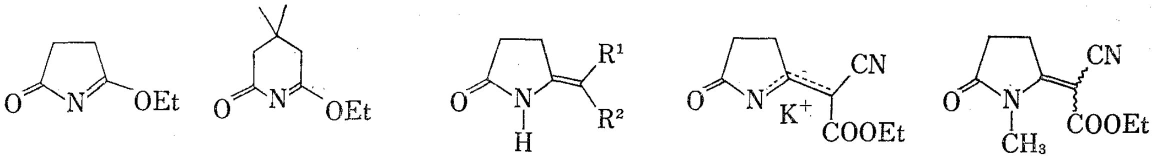
O-Ethyl succinimide (I) and O-ethyl 4,4-dimethylglutarimide (II) were reacted with active methylene compounds (ethyl cyanoacetate and ethyl acetoacetate), phenylhydrazine and its derivatives, and N-bromosuccinimide. Furthermore, the salt formation of the cyanoacetylidene compound (III), the hydrolysis of the acetoacetylidene compound (VIII), the Fischer indolization of the imidrazones (XIII and XIV), and the Favorskii rearrangement of the 3-bromo-imides (XX and XXI) were examined.

As to the reactions of O-alkylated imides, Comstock, *et al.*[3] reported the reaction of O-ethyl succinimide (I) with aniline, and Koch, *et al.*[4] communicated the photochemical behaviours of I and O-ethyl phthalimide. In our preceding paper,[5] the reductions of O-alkylated imides were discussed. In this paper, some other reactions of I and O-ethyl 4,4-dimethyl-glutarimide (II) are presented.

1) Reactions of I and II with Active Methylene Compounds

a) Reactions with Ethyl Cyanoacetate——Reaction of I with ethyl cyanoacetate in boiling ethanol gave ethyl 5-cyanoacetylidene-2-pyrrolidone (III) as colorless needles in quantitative yield. III was converted to the potassium salt (IV) by neutralization with one equivalent of potassium hydroxide in aqueous ethanol. IV was converted mostly to the isomer (V) of III by treatment with 10% hydrochloric acid solution. Assignment of these two geometrical isomers, III and V, was based on the infrared (IR) and nuclear magnetic resonance (NMR) spectra,[6] that is, in III the absorption bands due to an intramolecular hydrogen bond and ester carbonyl group were observed at 3320 and 1685 cm^{-1} respectively. On the other hand, V exhibited an ester carbonyl band at 1700 cm^{-1}, but no absorption band due to intramolecular hydrogen bond was observed. In NMR, a signal assigned to a proton of amide was observed at -0.51τ in III, and at 0.88τ in V.



I II III : R^1=CN, R^2=COOEt
V : R^1=COOEt, R^2=CN IV VI

Chart 1

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[1] *a*) A part of this work was presented at the 7th Congress of Heterocyclic Chemistry, Chiba, 1974. K. Matoba, S. Imoto, and T. Yamazaki, *Heterocycles*, 3, 77 (1975); *b*) Preceding paper: ref. 5) is regarded as part I.

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[3] S.J. Comstock and H.L. Wheeler, *Am. Chem. J.*, 13, 522 (1891).

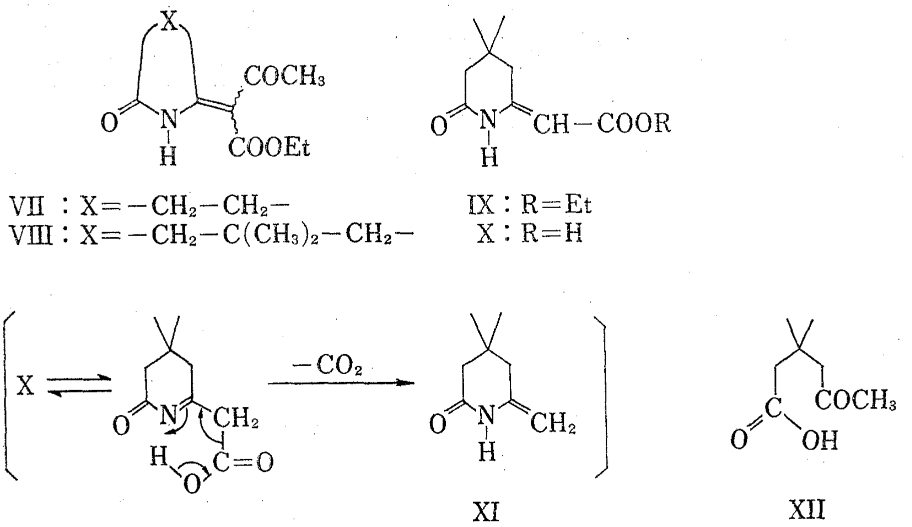
[4] *a*) T.H. Koch and R.J. Slusk, *Tetrahedron Letters*, **1970**, 2391; *b*) T.H. Koch and K.H. Howard, *ibid.*, **1972**, 4035.

[5] K. Matoba and T. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **22**, 2999 (1974).

[6] R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

Next, IV was treated with methyl iodide in connection with the interesting results observed in the reaction of ethyl 2-quinolyl cyanoacetate derivatives.[7] However, in this case, N-methylated compound, ethyl 1-methyl-5-cyanoacetylidene-2-pyrrolidone (VI) was obtained from IV as the sole product.

b) Reactions with Ethyl Acetoacetate——Reaction I or II with ethyl acetoacetate under the same conditions as those used for the preparation of III was unsuccessful. Thus ethyl 5-acetoacetylidene-2-pyrrolidone (VII) was obtained by heating I with ethyl acetoacetate at 100°. On the other hand, ethyl 6-acetoacetylidene-4,4-dimethyl-2-piperidone (VIII) could be obtained by heating II with the reagent in the presence of triethylamine. It was revealed from the NMR spectrum that VIII thus obtained was about 2:1 mixture of the geometrical isomers. Unfortunately we failed in the identification of these isomers.



VII : X = $-CH_2-CH_2-$

VIII : X = $-CH_2-C(CH_3)_2-CH_2-$

IX : R = Et

X : R = H

XI

XII

Chart 2

Baty, *et al.*[8] succeeded in converting ethyl 2-quinolylacetoacetate to ethyl 2-quinolylacetate by treating with sodium hydride in dimethyl cellosolve. However, treatment of VII or VIII with sodium hydride under the same conditions as those reported resulted in the complete recovery of the starting materials. On the other hand, 6-ethoxycarbonylmethylene-4,4-dimethyl-2-piperidone (IX) could be obtained by treating VIII with one molar equivalent of potassium hydroxide in aqueous ethanol. IX resisted to the catalytic reduction over Adams' catalyst or Raney nickel under ambient conditions. VIII was treated with an excess of potassium hydroxide in aqueous ethanol to give 6-carboxymethylene-4,4-dimethyl-2-piperidone (X) in 85% yield. An attempt to obtain 4,4-dimethyl-6-methylene-2-piperidone (XI) by decarboxylation of X under acidic conditions was unsuccessful. X was heated with dilute sulfuric acid for 3 hr to give a colorless oil, which was assigned to be 2,2-dimethyl-4-oxo-*n*-caproic acid (XII) from the spectral data and the elemental analysis.

2) Reactions with Phenylhydrazines

I reacted with phenylhydrazine at room temperature in ethanol to give phenylhydrazone (XIII). II also reacted with phenylhydrazine and its derivatives under the similar conditions to give the corresponding phenylhydrazones (XIVa—d). It was revealed that these products have the structures as shown by the elemental analyses and the physical data.

Refluxing XIVa with acetone in chloroform in the presence of silica gel for 4.5 hr gave the acetonide (XVa) in good yield. Similarly XIVb, more basic than XIVa, afforded the

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[7] T. Yamazaki, K. Matoba, and S. Imoto, *Heterocycles*, **4**, 713 (1976).

[8] J.D. Baty, G. Jones, and C. Moore, *J. Org. Chem.*, **34**, 3295 (1969).

corresponding acetonide (XVb) by refluxing for only 2.5 hr. In the absence of silica gel, XIVb gradually reacted with acetone and it took over 5 hr to complete the reaction. These acetonides, XVa and XVb, exhibited deep blue coloration on thin-layer chromatogram (TLC) by spraying the sulfuric acid solution of ceric sulfate.

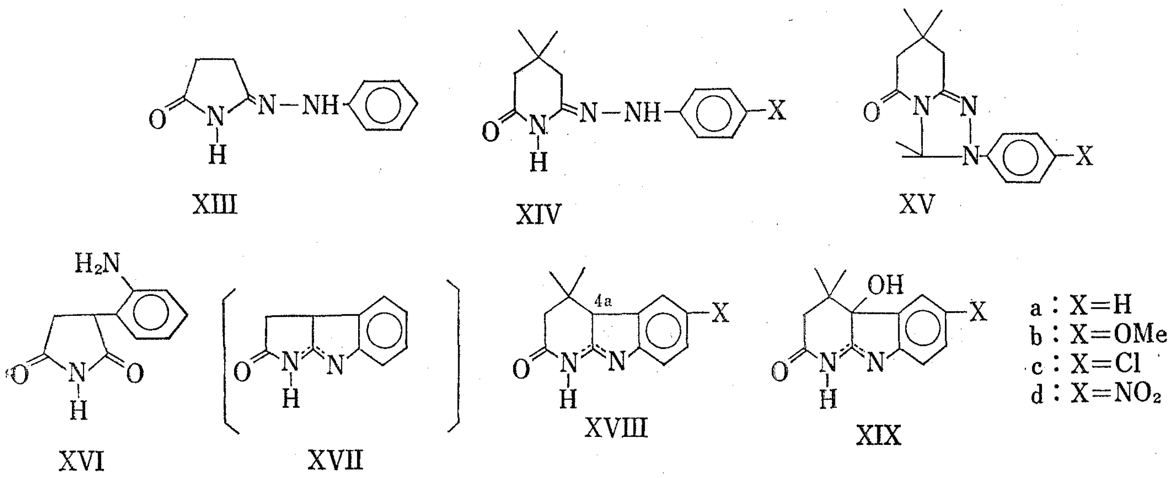

Chart 3

These phenylhydrazones, XIII and XIVa—d, were next subjected to the Fischer indolization. XIII was heated with 1.3 equivalents of borontrifluoride (BF_3) etherate in acetic acid for 4 hr to give a precipitate in poor yield. From the spectral data this product was suggested to be 3-(2-aminophenyl)succinimide (XVI), which would probably be formed through the hydration on the indolenine (XVII) followed by the ring cleavage. Then XIVa was treated with BF_3-etherate under the same conditions mentioned above to give a single product which was unstable and changed to stable one. The mode of this change could be detected on TLC. The elemental analysis and the mass spectrum of this stable product were consistent with $C_{13}H_{14}O_2N_2$, which corresponded to the oxidized form of the expected indolenine, 4,4-dimethyl-2-oxo-2,3,4,4a-tetrahydro-1H or 9H-pyrido[2,3-*b*] indole (XVIIIa). Based on the data reported by Hino, *et al.*,[9] the position 4a was suggested to be readily oxidized. Therefore, this stable product was 4a-hydroxy-4,4-dimethyl-2-oxo-2,3,4,4a-tetrahydro-1H or 9H-pyrido-[2,3-*b*]indole (XIXa), and the unstable one was therefore suggested to be XVIIIa. The next point especially have to be mentioned is on the NMR spectrum of XIXa; the difference in the chemical shifts of two protons at 3-position was about 1 ppm and that between two methyl groups at 4-position about 0.8 ppm. Taking the stereo-structure of XIXa into consideration, these large differences may probably be attributed to the anisotropy of the benzene ring. In case of XIVb, decomposition to the parent imide and *p*-methoxy-phenylhydrazine occurred prior to the cyclization to the indole derivative. XIXc was obtained from XIVc in a similar fashion to the case of XIVa, and in case of XIVd, the starting material was recovered. When this reaction was carried out in the presence of polyphosphoric acid or zinc chloride as Lewis acid instead of BF_3-etherate, the starting materials or the parent imides were obtained.

3) Reactions with N-Bromosuccinimide

A solution of I and N-bromosuccinmide in chloroform was refluxed to give a viscous oil, which was easily converted with water to an unstable oil. It was suggested from the physical data to be 3-bromo-succinimide (XX), which had been synthesized by treating succinimide directly with bromine in a sealed tube.[10] This latter known method, however, could not

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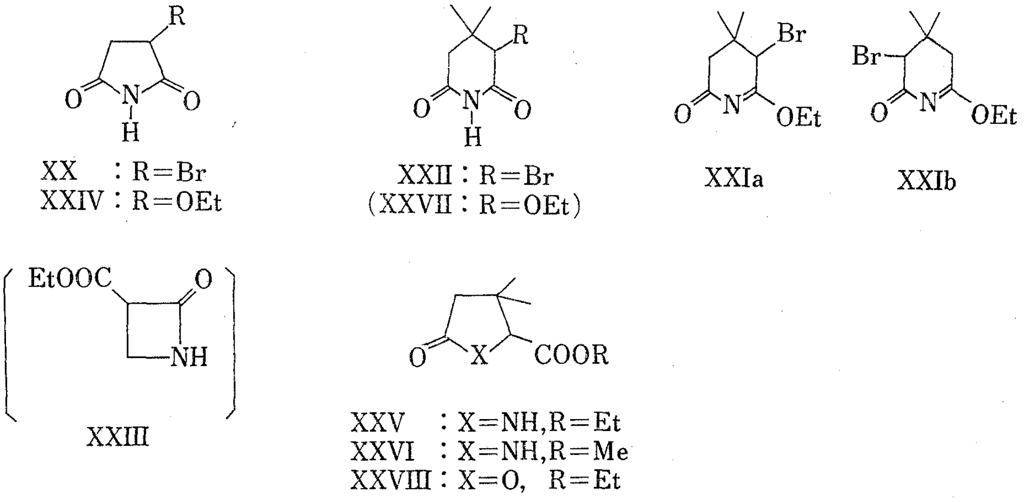
9) T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, and S. Yamada, *Tetrahedron*, **23**, 1441 (1967).
10) R. Kusserow, *Ann.*, **252**, 158 (1889).

avoid the formation of dibromo compound and the recovery of the starting material. Therefore, the method *via* iminoether was more preferable to the direct bromination. In a similar fashion, 3-bromo-4,4-dimethyl-glutarimide (XXII) was obtained in good yield *via* O-ethyl 3-bromo-4,4-dimethyl-glutarimide (XXIa) or O-ethyl 5-bromo-4,4-dimethyl-glutarimide (XXIb). XXII was a crystalline compound, mp 134—136°, and exhibited in the NMR spectrum a signal due to the proton at the carbon bearing bromine atom in doublet (J=1.5 cps) at 5.73τ coupled with the pseudoequatorial proton (7.60τ) at the 5-position. From this NMR data, it was revealed that the bromine atom was fixed in pseudo-axial position.[11]



XX : R=Br
XXIV : R=OEt

XXII : R=Br
(XXVII : R=OEt)

XXIa

XXIb

XXIII

XXV : X=NH, R=Et
XXVI : X=NH, R=Me
XXVIII : X=O, R=Et

Chart 4

On these bromo imides, XX and XXII, the Favorskii rearrangement was examined. The reaction conditions used were refluxing bromo-imide with 2.2 equivalents of sodium ethoxide in ethanol for 5 hr. In case of XX, it was concluded from the spectral data and the elemental analysis that the product was not the expected rearrangement product, β-lactam ester (XXIII), but the substituted product, 3-ethoxy-succinimide (XXIV). On the other hand, the product obtained from XXII exhibited in IR spectrum a carbonyl band at 1720 cm^{-1} and in NMR spectrum singlet signals due to amino proton, proton at the carbon bearing ester group, and methylene protons. From these data and the elemental analysis this product was suggested to be the expected rearrangement product, 5-carbethoxy-4,4-dimethyl-2-pyrrolidone (XXV). This was supported further by the fact that the corresponding methyl ester, 5-carbomethoxy-4,4-dimethyl-2-pyrrolidone (XXVI), showed the similar physical data to XXV. XXVI was obtained by treating 5-carboxy-4,4-dimethyl-2-pyrrolidone, the hydrolysis product of XXV, with diazomethane. Furthermore XXV could be converted to 5-carbethoxy-4,4-dimethyl-butyrolactone (XXVIII) by treating with ethanolic hydrochloric acid. In this case, the substituted product, 3-ethoxy-4,4-dimethyl-glutarimide (XXVII) was not obtained.

Experimental

All the melting points taken a Kofler block and the boiling points are uncorrected. The following equipments were used: IR spectra, Hitachi Grating Infrared 215 spectrometer; ultraviolet (UV) spectra, Hitachi EPS-2 spectrometer; NMR spectra, JEOL C-60H spectrometer with tetramethylsilane as an internal reference; GLC, Shimazu gas chromatograph Model GC-3AF (5% SE-30 column, N_2-gas, 40 ml/min); mass spectra, JEOL TMS-01SG (75 eV, direct inlet system). The TLC values were obtained with Kiesel gel G nach Stahl (Merck) as adsorbent. The spots were detected by spraying with 1% ceric sulfate-10% sulfuric acid and heating. For column chromatography, Wakogel C-200 was used. The chemical shifts and coupling constants

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[11] J. Meinwald and Y.C. Meinwald, *J. Am. Chem. Soc.*, **85**, 2514 (1963).

in NMR were described in τ-value and cps respectively. The abbreviations used to demonstrate coupling pattern are as follows: singlet-s, doublet-d, triplet-t, quartet-q, multiplet-m, broad-br. All the solvents were evaporated under reduced pressure.

Ethyl 5-Cyanoacetylidene-2-pyrrolidone (III)——A solution of O-ethyl succinimide (I)[5] and ethyl cyanoacetate (1.2 molar eq.) in EtOH was refluxed for 1 hr. After the evaporation of the solvent, the residual solid was purified by recrystallization from EtOH to give colorless needles in quantitative yield. mp 150—152°. TLC (acetone: $CHCl_3=1:1$): *Rf* 0.85. IR ($CHCl_3$) cm^{-1}: ν_{OH}3320, $\nu_{C\equiv N}$2220, $\nu_{C=O}$ and $\nu_{C=C}$1760, 1685, 1595. UV: λ_{max}^{EtOH} 276 mμ (ε; 22600). NMR ($CDCl_3$): -0.51 (1H, br. s, $\rangle$NH), 5.70 (2H, q, $J=7$, $-OCH_2-$), 6.60—7.00 and 7.15—7.55 (each 2H, pair of m, $-CH_2-CH_2-$), 8.66 (3H, t, $J=7$, $-CH_3$). *Anal.* Calcd. for $C_9H_{10}O_3N_2$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.40; H, 5.10; N, 14.31.

Potassium Salt of III (IV)——To III in EtOH one equivalent of KOH in EtOH was added at room temperature. After standing overnight, IV precipitated. Yield: quantitative. IV was easily soluble in water and slightly soluble in EtOH. mp 328—330° (from EtOH–H_2O). IR (Nujol) cm^{-1}: $\nu_{C\equiv N}$2200, $\nu_{C=O}$ and $\nu_{C=C}$ 1700, 1647, 1500. UV: λ_{max}^{EtOH} 309 mμ (ε; 23700). *Anal.* Calcd. for $C_9H_9O_3N_2K$: C, 46.59; H, 3.91; N, 12.08. Found: C, 46.35; H, 3.81; N, 11.92.

The Isomer of III (V)——To IV in water, 10% HCl solution was added to give precipitate. The solid collected by filtration was recrystallized from EtOH. V: mp 182—184°. Yield was about 80%. TLC (acetone: $CHCl_3=1:1$): *Rf* 0.85. IR ($CHCl_3$) cm^{-1}: ν_{OH} 3380, $\nu_{C\equiv N}$ 2230, $\nu_{C=O}$ 1780, 1700, 1620. UV: λ_{max}^{EtOH} 276 mμ (ε; 23600). NMR ($CDCl_3$): 0.88 (1H, br. s, $\rangle$NH), 5.75 (2H, q, $J=7$, $-OCH_2-$), 6.35—6.85 and 7.20—7.70 (4H, pair of m, $-CH_2-CH_2-$), 8.70 (3H, t, $J=7$, $-CH_3$). *Anal.* Calcd. for $C_9H_{10}O_3N_2$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.37; H, 5.16; N, 14.27.

Ethyl 1-Methyl-5-cyanoacetylidene-2-pyrrolidone (VI)——IV was treated with an excess mole of methyl iodide in a sealed tube at 100—120° for 48 hr. Evaporation of the excess reagent gave a solid mass. Yield: quantitative. mp 120—122° (from benzene–*n*-hexane). TLC (acetone: $CHCl_3=1:1$) *Rf* 0.85. IR (Nujol) cm^{-1}: $\nu_{C\equiv N}$ 2220, $\nu_{C=O}$ and $\nu_{C=C}$ 1755, 1710, 1560. UV: λ_{max}^{EtOH} 283 mμ (ε; 29300). NMR ($CDCl_3$): 5.70 (2H, q, $J=7$, $-OCH_2-$), 6.43 (3H, s, $\rangle N-CH_3$), 6.40—6.80 and 7.15—7.55 (4H, pair of m, $-CH_2-CH_2-$), 8.65 (3H, t, $J=7$, $-CH_3$). *Anal.* Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.50; H, 5.90; N, 13.40.

Ethyl 5-Acetoacetylidene-2-pyrrolidone (VII)——I (500 mg) and ethyl acetoacetate (1.1 molar eq.) was heated on a water bath at 100° for 5 hr. After standing overnight, the reaction mixture solidified. mp 83—85° (from *n*-hexane–benzene). Yield: *ca.* 400 mg. IR (Nujol) cm^{-1}: ν_{NH} 3210, $\nu_{C=O}$ 1765, 1690, 1620. UV: λ_{max}^{EtOH} 286.5 mμ (ε; 10100). NMR ($CDCl_3$): -1.8 (1H, br. s, $\rangle$NH), 5.68 (2H, q, $J=7$, $-OCH_2-$), 6.50—6.95 and 7.25—7.70 (each 2H, pair of m, $-CH_2-CH_2-$), 7.57 (3H, s, $-COCH_3$), 8.63 (3H. t, $J=7$, $-CH_2\underline{CH_3}$). *Anal.* Calcd. for $C_{10}H_{13}O_4N$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.60; H, 6.32; N, 6.56. VII was refluxed with 1.15 mole eq. of NaH in dimethyl cellosolve for 30 min. After evaporation of the solvent VII was recovered exclusively.

Ethyl 6-Acetoacetylidene-4,4-dimethyl-2-piperidone (VIII)——A mixture of II (3.7 g), ethyl acetoacetate (4.5 g), and triethylamine (6.5 g) was heated at 100° for 34 hr in a sealed tube. After evaporation of triethylamine, the residue was fractionated through silica gel column. An excess of ethyl acetoacetate was recovered from *n*-hexane fraction and VIII was isolated from benzene fraction followed by distillation. bp 150° (1 mmHg). Yield: 2.5 g. IR (film) cm^{-1}: ν_{NH} 3240, $\nu_{C=O}$ 1700, 1665, 1635, 1580. UV: λ_{max}^{EtOH} 296 mμ (ε; 14200). NMR (CCl_4): -2.28 and -1.05 (2: 1 in 1H, each br. s, $\rangle$NH), 5.71 (2H, q, $J=7$, $-OCH_2-$), 7.55 and 7.68 (4H, nearly s, $2\times CH_2\langle$), 7.70 and 7.80 (1: 2 in 3H, each s, $-COCH_3$), 8.65 (3H, t, $J=7$, $-CH_2\underline{CH_3}$), 8.91 and 8.93 (2: 1 in 6H, each s, geminal CH_3). *Anal.* Calcd. for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.91; H, 7.81; N, 5.82. VIII was unaffected to NaH under the conditions as described in the case of VII.

6-Ethoxycarbonylmethylene-4,4-dimethyl-2-piperidone (IX)——VIII was treated with 1 mole eq. of methanolic KOH solution at room temperature for 2 days. The mixture was diluted with water and acidified with 5% HCl solution followed by the extraction with ether. Concentration of dried ether extract gave IX as a viscous oil, which was purified by distillation. bp 134—136° (5 mmHg). Yield: 85%. IR (film) cm^{-1}: ν_{NH}3280, $\nu_{C=O}$1670, 1625. UV: λ_{max}^{EtOH} 270.5 mμ (ε; 19800). NMR (CCl_4): -0.49 (1H, br. s, $\rangle$NH), 5.25 (1H, nearly s, vinylic H), 5.87 (2H, q, $J=7$, $-OCH_2-$), 7.73 (4H, nearly s, $2\times CH_2\langle$), 8.73 (3H, t, $J=7$, $-CH_2\underline{CH_3}$), 8.93 (6H, s, geminal CH_3). Anal. Calcd. for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.38; H, 7.87; N, 6.87. This ester resisted to the catalytic hydrogenation over Adams' catalyst or Raney Ni under the ordinary pressure.

6-Carboxymethylene-4,4-dimethyl-2-piperidone (X)——VIII was treated with an excess of 4.5% methanolic KOH at room temperature for 2 days. After evaporation of MeOH at low temperature as possible, the residue was dissolved in water and acidified with 5% HCl solution. Ether extract was dried over $MgSO_4$ and the solvent was distillied off to give a solid mass. mp 136—137° (from benzene). The yield was quantitative. IR (Nujol) cm^{-1}: ν_{NH}3230, $\nu_{C=O}$1700, 1610. UV: λ_{max}^{EtOH} 268 mμ (ε; 17700). NMR ($CDCl_3$): -0.61 (1H, br. s, $\rangle$NH), 1.50 (1H, br. s, $-COOH$), 5.04 (1H, t, $J=0.7$, vinylic H), 7.63 (4H, s, $2\times CH_2\langle$), 8.93 (6H, s, geminal CH_3). *Anal.* Calcd. for $C_9H_{13}O_3N$: C, 59.00; H, 7.15: N7.65. Found: C, 58.75; H, 7.14; N, 7.57.

2,2-Dimethyl-4-oxo-*n*-caproic Acid (XII)——X was heated with 10% H_2SO_4 on a water bath for 3 hr. The mixture was extracted with ether, which was dried over $MgSO_4$. After the solvent was evaporated, the residue was micro-distilled. bp<150° (5 mmHg). Yield: 55%. IR (film) cm^{-1}: $\nu_{C=O}$ 1715. NMR ($CDCl_3$–

CCl_4): −0.40 (1H, br. s, –COOH), 7.45 and 7.52 (each 2H, s, $>CH_2$), 7.91 (3H, s, $-COCH_3$), 8.90 (6H, s, geminal CH_3). Mass Spectrum *m/e*: 158 (M^+). *Anal.* Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.55; H, 8.99.

1-Phenyl-2-(5-oxo-2-pyrrolid-1-enyl)-hydrazine (XIII)——To I (6.6 g, 46 mmoles) in EtOH, phenylhydrazine (5 g, 46 mmoles) in EtOH was added. After warmed for 5 min on a water bath, the reaction mixture was stood overnight in an ice bath to give precipitates which were collected on a filter. Recrystallization from EtOH gave XIII. Yield: 7.9 g. mp 166—168°. IR (Nujol) cm^{-1}: ν_{NH}3350, 3200, 3090, $\nu_{C=O}$1721, $\nu_{C=N}$1688, $\nu_{C=C}$1602. NMR ($CDCl_3$): 2.52—3.25 (5H, m, aromatic H), 7.00—7.63 (4H, m, aliphatic H). *Anal.* Calcd. for $C_{10}H_{11}ON_3$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.34; H, 5.78; N, 22.49.

1-Phenyl-2-(4,4-dimethyl-6-oxo-2-piperid-1-enyl)-hydrazine (XIVa)——II (8 g, 46 mmoles) and phenylhydrazine (5 g, 46 mmoles) were treated in the same manner mentioned for XIII to give XIVa. Yield: 9.8 g. mp 226—228° (from EtOH). IR (Nujol) cm^{-1}: ν_{NH}3370, 3212, 3090, $\nu_{C=O}$ and $\nu_{C=N}$ 1695, $\nu_{C=C}$1600. NMR ($CDCl_3$): 2.75—2.96 (5H, m, aromatic H), 7.62 (4H, m, $2\times CH_2<$), 9.04 (6H, s, $2\times CH_3-$). *Anal.* Calcd. for $C_{13}H_{17}ON_3$: C, 67.50; H, 7.41; N, 18.17. Found: C, 67.31; H, 7.32; N, 18.05.

1-(4-Methoxy-phenyl)-2-(4,4-dimethyl-6-oxo-2-piperid-1-enyl)-hydrazine (XIVb)——From II (6.1 g, 36 mmoles) and 4-methoxy-phenylhydrazine[12] (5 g, 36 mmoles), XIVb (6.6 g) was obtained. XIVb: mp 143—145° (from EtOH). IR (Nujol) cm^{-1}: ν_{NH} 3370, 3200, 3080, $\nu_{C=O}$ and $\nu_{C=N}$1690—1645, $\nu_{C=C}$ 1605, 1602. NMR (d_5-pyridine): 2.65 (2H, d, $J=9$, aromatic H), 2.90 (2H, d, $J=9$, aromatic H), 6.30 (3H, s, $-OCH_3$), 7.35—7.75 (4H, m, $2\times CH_2<$), 9.05 (6H, s, $2\times CH_3$). *Anal.* Calcd. for $C_{14}H_{19}O_2N_3$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.17; H, 7.58; N, 15.81.

1-(4-Chloro-phenyl)-2-(4,4-dimethyl-6-oxo-2-piperid-1-enyl)-hydrazine (XIVc)——II (5.9 g, 35 mmoles) was condensed with 4-chloro-phenylhydrazine[13] (5 g, 35 mmoles) to give XIVc (6.3 g). mp 208—208.5° (from EtOH). IR (Nujol) cm^{-1}: ν_{NH} 3350, 3180, 3070, $\nu_{C=O}$ and $\nu_{C=N}$ 1682—1640, $\nu_{C=C}$ 1598. NMR($CDCl_3$–d_5-pyridine): 2.95 (4H, d.d, $J=12$, 9, aromatic H), 7.64 (4H, m, $2\times CH_2-$), 9.01 (6H, s, $2\times CH_3$). *Anal.* Calcd. for $C_{13}H_{16}ON_3Cl$: C, 58.81; H, 6.08; N, 15.83. Found: C, 59.04; H, 5.85; N, 15.92.

1-(4-Nitrophenyl)-2-(4,4-dimethyl-6-oxo-2-piperid-1-enyl)-hydrazine (XIVd)——II (5 g, 33 mmoles) and 4-nitro-phenylhydrazine (5 g, 33 mmoles) was condensed in a usual manner to give XIVd. Yield: 6.2 g. mp 265—267°. IR (Nujol) cm^{-1}: ν_{NH} 3340, 3210, 3090, $\nu_{C=O}$ and $\nu_{C=N}$ 1700—1600, $\nu_{C=C}$ 1595, ν_{NO} 1550, 1360. NMR ($CDCl_3$-d_5-pyridine): 1.86 (2H, d, $J=9$, aromatic H), 2.88(2H, d, $J=9$, aromatic H). 4.97 (2H, br. s, $2\times NH<$), 7.60 (4H, m, $2\times CH_2<$), 9.07 (6H, s, $2\times CH_3-$). *Anal.* Calcd. for $C_{13}H_{16}O_3N_4$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.71; H, 6.11; N, 20.29.

Acetonide of XIVa (XVa)——A solution of XIVa (500 mg) and silica gel (10 g) in acetone–$CHCl_3$ (1: 9, 100 ml) was refluxed for 4.5 hr. After separation of silica gel by filtration the solvent was distilled off. Ether soluble part of this residue was recrystallized from *n*-hexane. XVa: mp 104—105°. Yield: *ca.* 300 mg. IR (Nujol) cm^{-1}: $\nu_{C=O}$ and $\nu_{C=N}$ 1690, 1650, 1600. NMR ($CDCl_3$): 2.50—3.25 (5H, m, aromatic H), 7.52 and 7.68 (each 2H, s, $CH_2<$), 8.21 and 8.92 (each 6H, s, geminal CH_3). *Anal.* Calcd. for $C_{16}H_{21}ON_3$: C, 70.82; H, 7.80; N, 15.49. Found: C, 71.14; H, 7.66; N, 15.28. Under the conditions mentioned above, the ratio of XIVa to XVa after refluxing for 1.25 hr was 3: 1 and 1: 1 after 2 hr refluxing.

Acetonide of XIVb (XVb)——A solution of XIVb (500 mg) and silica gel (10 g) in acetone–$CHCl_3$ (1: 9, 100 ml) was refluxed for 2 hr. After work-up as above, ether soluble part of this residue was recrystallized from ether–*n*-hexane. XVb: mp 105—107°. Yield: 300 mg. TLC ($CHCl_3$): *Rf* 0.7 (green coloration by spraying of ceric sulfate solution). IR (Nujol) cm^{-1}: $\nu_{C=O}$ and $\nu_{C=N}$ 1680, 1645. NMR (CCl_4): 3.00 and 3.27 (each 2H, A_2B_2, $J=9$, aromatic H), 6.26 (3H, s, $-OCH_3$), 7.60 and 7.78 (each 2H, s, $>CH_2$), 8.34 and 8.89 (each 6H, s, geminal CH_3). *Anal.* Calcd. for $C_{17}H_{23}O_2N_3$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.80; H, 7.73; N, 13.74. Mass Spectrum *m/e*: 301 (M^+, base peak). In the presence of silica gel, the ratio of XIVb to XVb was 1: 3 after refluxing for 1.25 hr, and after 2.5 hr only XVb was detected on TLC. In the absence of silica gel, on the other hand, after refluxing for 1.25 hr the ratio of XIVb to XVb was 5: 1, and 4: 1 after 2.5 hr refluxing. In this case after refluxing for 5.25 hr, XIVb disappeared and only XVb was detected on TLC.

General Procedure of Fischer Indolization——BF_3-etherate (excess mole) was added to the phenylhydrazone derivatives, XIII and XIVa—d, in AcOH. After heating for several hr at 90°, AcOH was evaporated. The residue was dissolved in water and extracted with ether and AcOEt, which were washed with 5% Na_2CO_3 solution and water. The basic combined aqueous solution was extracted with AcOEt. Each organic layers were dried over $MgSO_4$ and solvents were removed.

2-(2-Aminophenyl)succinimide (XVI)——XIII (1 g) was treated under the general procedure of Fischer indolization (BF_3-etherate: 6 molar eq., 15 hr). The product obtained from the first AcOEt fraction was purified through silica gel column. The crystals eluted with ether was recrystallized from ether–acetone. XVI: TLC (acetone: $CHCl_3$=1: 1): *Rf* 0.6. Yield: 25 mg. mp 160—163°. IR (Nujol) cm^{-1}: ν_{NH} 3280, $\nu_{C=O}$ 1780—1700, $\nu_{C=C}$ 1602. Mass Spectrum *m/e*: 190 (M^+).

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13) G.H. Coleman, "Organic Syntheses," Coll. Vol. I, ed. by H. Gilman, John Wiley and Sons, Inc., New York, N.Y., 1944, p. 442.

4a-Hydroxy-4,4-dimethyl-2-oxo-2,3,4,4a-tetrahydro-1H or 9H-Pyrido[2,3-*b*]indole (XIXa)——XIVa (1 g) was treated with BF_3-etherate (1.6 molar eq.) for 5 hr. Reaction conditions and methods of work-up were the same as those of the general procedure. The product, 4,4-dimethyl-2-oxo-2,3,4,4a-tetrahydro-1H or 9H-pyrido[2,3-*b*]indole (XVIIIa), exhibited a purple spot at *Rf* 0.6 in TLC (acetone: $CHCl_3=1:1$) and was converted to XIXa through the purification using silica gel column. XIXa exhibited a brown spot at *Rf* 0.5. This product was obtained from ether layer together with the starting material, XIVa (150 mg). XIXa: 450 mg, 246—247° (from acetone). IR (Nujol) cm^{-1}: ν_{NH} 3150, $\nu_{C=O}$ 1703, $\nu_{C=N}$ 1638, $\nu_{C=C}$ 1602. NMR (d_5-pyridine): 2.30—3.10 (4H, m, aromatic H), 6.60 (1H, d, $J=18$, $>C\underline{H}_AH_B$), 7.59 (1H, d, $J=18$, $>CH_A\underline{H}_B$), 8.50 and 9.28 (each 3H, s, $-CH_3$). *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.72; H, 5.95; N, 12.03. Mass Spectrum *m/e*: 230 (M^+).

6-Chloro-4a-hydroxy-4,4-dimethyl-2-oxo-2,3,4,4a-tetrahydro-1H or 9H-Pyrido [2,3-*b*]indole (XIXc)——XIVc (1 g, 3.8 mmoles) in 30 ml AcOH was treated with BF_3-etherate (10 mmoles) for 5 hr. Combined AcOEt and ether extract was purified through silica gel column. XIVc (150 mg) and XIXc (400 mg) were eluted by ether and $CHCl_3$ respectively. XIXc: mp 252—254°. IR (Nujol) cm^{-1}: ν_{NH} 3150, $\nu_{C=O}$ 1703, $\nu_{C=N}$ 1631, $\nu_{C=C}$ 1600. NMR (d_5-pyridine): 2.33 (1H, m, aromatic H), 2.65 (2H, m, aromatic H), 5.10 (2H, br, $>NH+-OH$), 6.61 (1H, d, $J=18$, $>C\underline{H}_AH_B$), 7.59 (1H, d, $J=18$, $>CH_A\underline{H}_B$), 8.54 (3H, s, $-CH_3$), 9.29 (3H, s, $-CH_3$). *Anal.* Calcd. for $C_{13}H_{13}O_2N_2Cl\cdot 1/2H_2O$: C, 57.03; H 5.12; N, 10.24. Found: C, 56.56; H, 4.72; N, 10.23. Mass Spectrum *m/e*: 264 (M^+, base peak), 266 (M^++2, 36.2%).

3-Bromo-succinimide (XX)——A solution of I (4.5 g), NBS (6.3 g), and benzoylperoxide (0.1 g) in CCl_4 was refluxed. After cool, the succinimide precipitated was collected by filtration and the solvent was distilled off, when a viscous oil was obtained. The yield was quantitative. O-Ethyl 3-bromo-succinimide: bp 135—142° (1 mmHg). IR (film) cm^{-1}: $\nu_{C=O}$ 1725, 1710, 1580. NMR (CCl_4+CDCl_3): 5.10—5.70 (3H, m, $-OCH_2-+>CH-Br$), 8.52 (3H, t, $J=7$, $-CH_3$). The suspension in water of this intermediate was heated for a few minutes to give homogeneous solution. The solution was extracted with $CHCl_3$ repeatedly. Concentration of dried extract afforded an oil which was micro-distilled. XX: bp<100° (3 mmHg), yellow viscous oil. XX was unstable[10] and turned gradually deep red in colour. IR (film) cm^{-1}: $\nu_{C=O}$ 1795 (weak), 1720. NMR (CCl_4): 5.15—6.15 (3H, m, $>CH-Br+-OCH_2-$), 6.80—7.20 and 7.25—7.65 (2H, pair of m, $>CH_2$), 8.67 (3H, t, like, $-CH_3$).

O-Ethyl 3- or 5-Bromo-4,4-dimethyl-glutarimide (XXIa or XXIb)——A solution of II (4 g), NBS (4 g), and benzoylperoxide (0.1 g) in CCl_4 was refluxed overnight. Succinimide was filtered off after cooling. From the filtrate a relatively stable oil was obtained. XXI: bp 114—117° (4 mmHg), yield was good. IR (film) cm^{-1}: $\nu_{C=O}$ 1700, $\nu_{C=N}$ 1580. NMR (CCl_4): 5.60 (2H, q, $J=7$, $-OCH_2-$), 5.82 (1H, d, $J=1$, $>CH-Br$), 7.64 (2H, AB like, $J=16$, $>CH_2$), 8.60 (3H, t, $J=7$, $-CH_2\underline{CH_3}$), 8.76 and 8.82 (each 3H, s, geminal CH_3).

3-Bromo-4,4-dimethyl-glutarimide (XXII)——XXI was treated with water at room temperature to give fine needles. XXII: mp 134—136° (from water), yield was quantitative. IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1713, 1680. NMR ($CDCl_3$): 1.20 (1H, br. s, $>NH$), 5.73 (1H, d, $J=1.5$, $>CH-Br$), 7.20 (1H, d, $J=18$, $>C\underline{H}_AH_B$), 7.60 (1H, d.d, $J=18$, 1.5, $>CH_A\underline{H}_B$), 8.72 (6H, s, geminal CH_3). *Anal.* Calcd. for $C_7H_{10}O_2NBr$: C, 38.21; H, 4.58; N, 6.37. Found: C, 38.48; H, 4.24; N, 6.62.

3-Ethoxy-succinimide (XXIV)——A solution of XX and NaOEt (2.2 molar eq.) in EtOH was refluxed for 5 hr. EtOH was evaporated and the residue dissolved in water was acidified with 10% HCl followed by the extraction with $CHCl_3$. $CHCl_3$ extract was dried and evaporated. GLC (150°): t_R 8 min (93%, XXIV). XXIV: bp <150° (3 mmHg). IR (film) cm^{-1}: $\nu_{C=O}$ 1720, 1790. NMR (CCl_4): 0.48 (1H, br. s, $>NH$), 5.72, 7.15, and 7.45 (3H, ABX type, $J=18$, 9.5, $-CH_2-CH(OEt)-$), 8.77 (3H, t, $J=6.5$, $-CH_3$). *Anal.* Calcd. for $C_6H_9O_3N$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.45; H, 6.33; N, 9.69. XXIV was dissolved in water and the solution was basified with 5% KOH solution and then saturated $AgNO_3$ solution was added. The mixture turned to acidic and the silver salt of XXIV precipitated. mp >300°. Next XXIV was treated with diazomethane etherate to afford 1-methyl-3-ethoxy-succinimide. IR (film) cm^{-1}: $\nu_{C=O}$ 1780 (weak), 1700. NMR ($CDCl_3$): 6.98 (3H, s, $>N-CH_3$), 8.72 (3H, t, $J=7$, $-CH_2\underline{CH_3}$). Mass Spectrum *m/e*: 157 (M^+).

5-Carbethoxy-4,4-dimethyl-2-pyrrolidone (XXV)——XXII in EtOH was treated with NaOEt (2.2 molar eq.) at reflux temperature for 16 hr. EtOH was distilled off and the residue was acidified with 5% HCl solution and extracted with ether. Ether was evaporated after drying. TLC ($CHCl_3$: EtOH=9: 1): *Rf* 0.8 (XXV, *ca.* 70%), 0.7 (unidentified product, *ca.* 30%). The crude oil was purified through silica gel column. XXV was eluted with benzene and micro-distilled. XXV: bp<100° (3 mmHg). IR (film) cm^{-1}: ν_{OH} 3500, $\nu_{C=O}$ 1795, 1720. NMR (CCl_4): 5.74 (2H, q, $J=7.5$, $-OCH_2-$), 6.10 (1H, s, $>CHN<$), 6.54 (1H, br. s, $>NH$), 7.59 (2H, nearly s, $>CH_2$), 8.64 (3H, t, $J=7.5$, $-CH_2C\underline{H}_3$), 8.83 and 8.92 (each 3H, s, geminal CH_3). *Anal.* Calcd. for $C_9H_{15}O_3N$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.52; H, 8.07; H, 7.53. Mass Spectrum *m/e*: 185 (M^+), 111 ($M^+-COOEt$, base peak).

5-Carbomethoxy-4,4-dimethyl-2-pyrrolidone (XXVI)——XXV was stood still for several days at room temperature to give the corresponding acid, 5-carboxy-4,4-dimethyl-2-pyrrolidone. IR (film) cm^{-1}: ν_{OH} 3470 (broad), $\nu_{C=O}$ 1710 (broad), 1640. This acid was treated with an excess of diazomethane etherate. Ether was evaporated after standing overnight and the residue was micro-distilled. XXVI: bp <150° (7 mmHg). TLC ($CHCl_3$: EtOH=9: 1): *Rf* 0.8 (this spot could not be distinguished from that of XXV even by means of co-spot technique). GLC (170°): t_R 2.6 min (*cf* XXV: t_R 3.3 min). IR (film) cm^{-1}: ν_{OH} 3450 (broad), $\nu_{C=O}$

1785, 1730. NMR (CCl_4): 6.21 (3H, s, $-OCH_3$), 6.68 (1H, br. s, $>NH$), 7.62 (2H, s, $>CH_2$), 8.84 and 8.92 (each 3H, s, geminal CH_3). *Anal.* Calcd. for $C_8H_{13}O_3N$: C, 56.12; H, 7.65; N, 8.18. Found: C, 56.04; H, 7.64; N, 8.28.

5-Carbethoxy-4,4-dimethyl-butyrolactone (XXVIII)——XXV was treated with ethanolic HCl solution for 2 hr at refluxing temperature. After the removal of precipitated NH_4Cl by filtration, the filtrate was concentrated to give an oil which was extracted with ether. GLC (170°): t_R 3.2 min. TLC ($CHCl_3$: acetone = 1 : 1): *Rf* 0.9. bp <150° (3 mmHg). Yield was nearly quantitative. IR (film) cm^{-1}: $\nu_{C=O}$ 1795, 1743. NMR (CCl_4): 5.58 (1H, s, $-OCH<$), 5.77 (2H, q, $J=7.5$, $-OCH_2-$), 7.67 (2H, AB type, $J=18$, $>CH_2$), 8.66 (3H, t, $J=7.5$, $-CH_2\underline{CH_3}$), 8.66 and 8.88 (each 3H, s, geminal CH_3). *Anal.* Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.76; H, 7.58.

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