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Studies on Ketene and Its Derivatives. LXVI.[1] Reaction of Acetoacetamide with α,β-Unsaturated Esters

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Michael addition reaction of acetoacetamide (I) with α,β-unsaturated esters (IIa—d), such as ethyl acrylate (IIa), ethyl crotonate (IIb), ethyl methacrylate (IIc), and ethyl cinnamate (IId) afforded 3-acetylglutarimide (IIIa), 3-acetyl-4-methylglutarimide (IIIb), 3-acetyl-5-methylglutarimide (IIIc), and 3-acetyl-4-phenylglutarimide (IIId) respectively.

In the case of ethyl acrylate (IIa), diethyl-4-carbamoylpimerate (IV), 3-ethoxycarbonylethylglutarimide (V), 3-acetyl-3-ethoxycarbonylethylglutarimide (VI) and 3-acetyl-5-ethoxycarbonylethylglutarimide (VII) were isolated as by-products besides IIIa.

Some reactions of 3-acetylglutarimide (IIIa), such as hydrolysis, ammonolysis, acylation, and alkylation are also described.

It is reported that cyanoacetamide reacted with ethyl acrylate (IIa) to give 3-cyanoglutarimide.[3,4] This reaction involves Michael addition of IIa to the active methylene of cyanoacetamide followed by ring-closure to give glutarimide derivative. While investigating of some potential uses of acetoacetamide (I), which is most easily prepared from diketene and ammonia, it occurred to us that Michael reaction of I with II might give glutarimide derivatives, which is the subject of the present paper.

When acetoacetamide (I) was allowed to react with ethyl acrylate (IIa), five crystalline products were obtained; *i.e.*, 3-acetylglutarimide (IIIa), diethyl 4-carbamoylpimelate (IV), 3-ethoxycarbonylethylglutarimide (V), 3-acetyl-3-ethoxycarbonylethylglutarimide (VI), and 3-acetyl-5-ethoxycarbonylethylglutarimide (VII). Reaction conditions such as solvent, catalyst, reaction temperature considerably influenced the product formed. For instance, reaction at room temperature in the presence of sodium ethoxide afforded IIIa, IV and V, while at reflux in the presence of sodium ethoxide or potassium *tert*-butoxide gave rise to IIIa in good yield. Moreover, as described in experimental section, the reaction in the presence of potassium *tert*-butoxide under a certain condition gave rise to VI and VII besides IIIa: see the 3rd run in experimental.

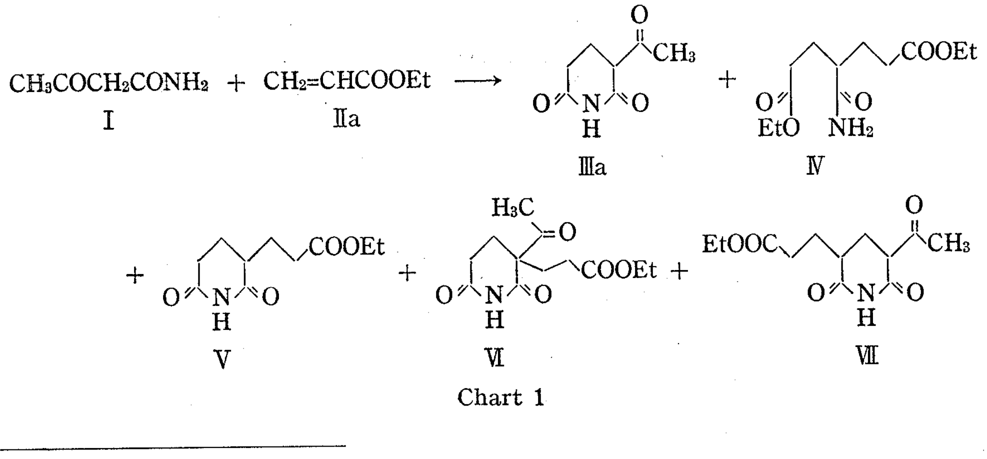

Chart 1

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[1] Part LXV: T. Kato, Y. Yamamoto, and S. Takeda, *Yakugaku Zasshi*, **94**, 627 (1974).

[2] Location: *Aobayama, Sendai, 980, Japan.*

[3] C. Mannich and P. Mohs, *Chem. Ber.*, **62**, 608 (1930).

[4] C. Barat, *J. Indian. Chem. Soc.*, **8**, 37 (1931).

Elemental analysis, infrared (IR) and nuclear magnetic resonance (NMR) data, and chemical reactions were well consistent with these structures. Namely, hydrolysis of IIIa with acid gave rise to 5-oxo-hexanoic acid (X).⁵⁾ Treatment with diluted alkali at room temperature afforded a hydrolysed product, to which 4-carbamoyl-5-oxo-hexanoic acid (XI) or its isomer 4-carboxy-5-oxo-hexanamide ($CH_5 \cdot CO \cdot CH(CO_2H) \cdot C_2H_5 \cdot CO \cdot NH_2$), could be given as the structure. Since the latter is the free acetoacetic acid structure, we preferred the former XI as a reasonable one. Hydrolysis with conc. alkali such as 50% KOH gave glutaric acid (XII).⁶⁾ Reaction of IIIa with acetyl chloride afforded 3-(1-acetoxyethylidene)-glutarimide (XIII).⁷⁾

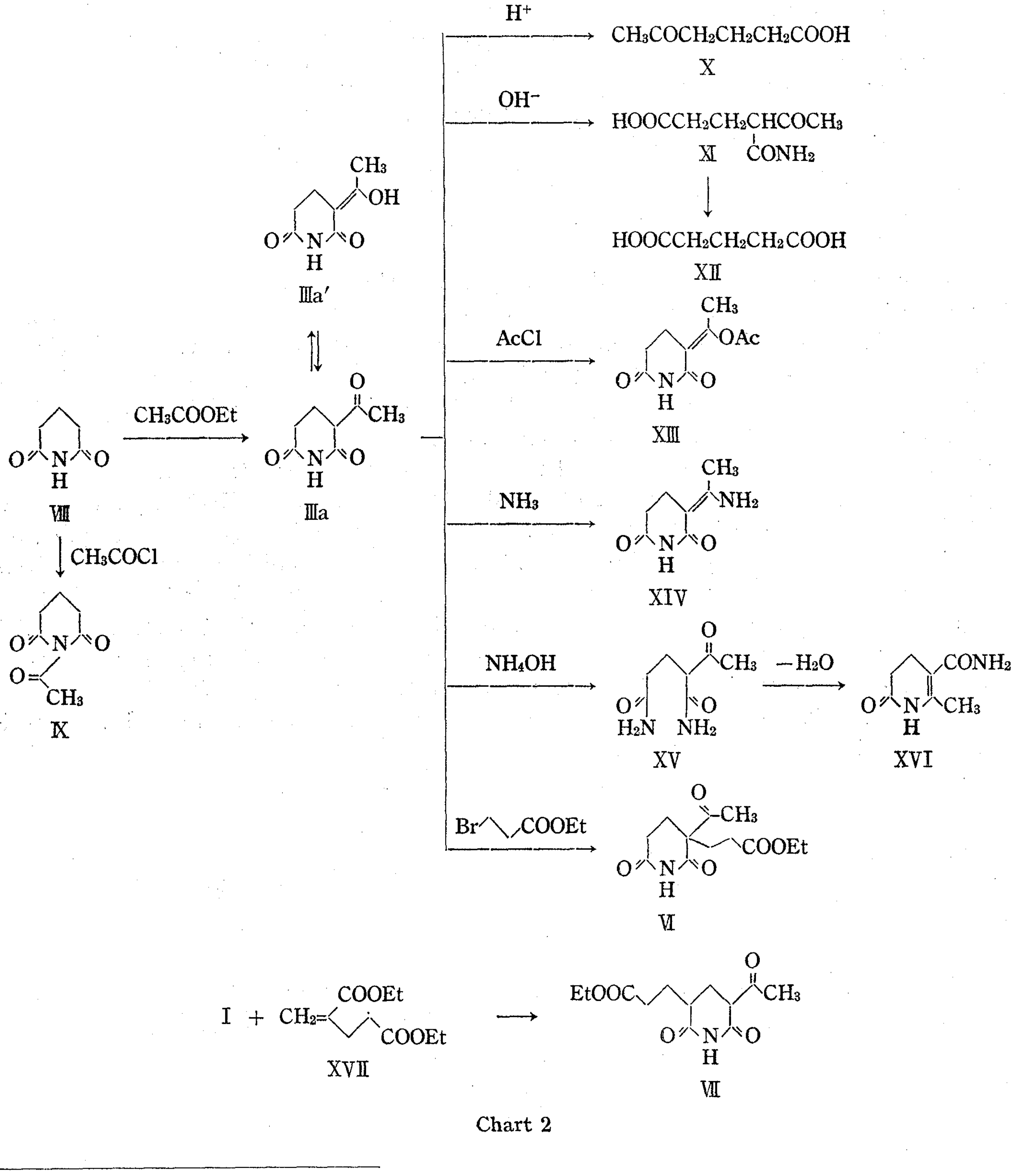

Chart 2

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5) A. Lipp, *Chem. Ber.*, **18**, 3281 (1885).

6) C.S. Marvel and W.F. Tuley, "Organic Synthesis," Coll. Vol. 1, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1956, p. 289.

7) T. Kato, H. Yamanaka, H. Fukumi, and M. Noda, *Yakugaku Zasshi*, **93**, 1437 (1973).

Treatment of IIIa with ethanolic ammonia gave 3-acetimidoylglutarimide (XIV),7) while reaction of IIIa with aqueous ammonia resulted in the ring-opening to afford 2-acetylglutaramide (XV), which then cyclized to give 6-methyl-3,4-dihydro-2(1*H*)-pyridone-5-carboxamide (XVI).8) These reactions are consistent with the structure IIIa as 3-acetylglutarimide, which, on spectral studies, exists mainly as an enol isomer (IIIa'). Applying the procedure reported by Hauser, *et al.*,9) an authentic sample of IIIa was prepared by the reaction of glutarimide (VIII) with ethyl acetate in liq. ammonia using lithium amide as a catalyst. It is of interest to note the use of acetylchloride in place of ethyl acetate afforded 1-acetylglutarimide (IX).

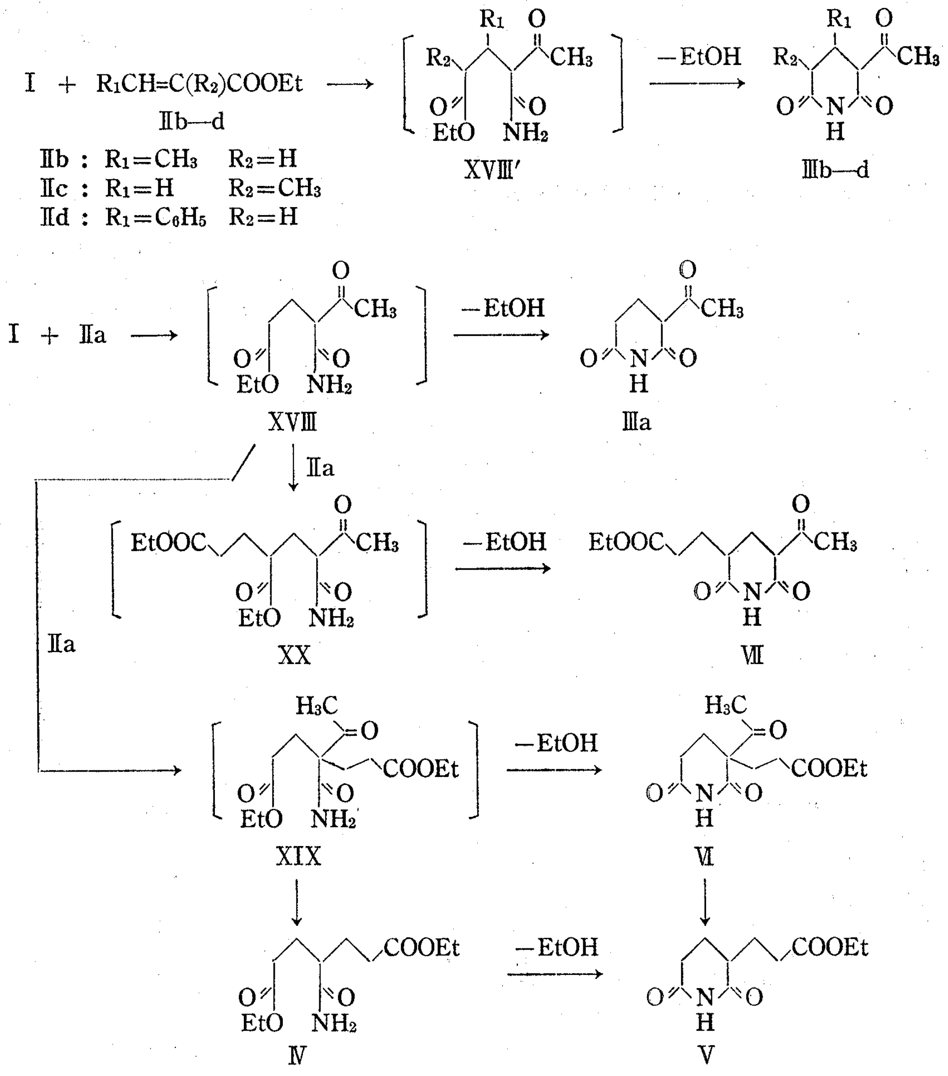

Chart 3

Reaction of IIIa with ethyl 3-bromopropionate gave 3-acetyl-3-ethoxycarbonylethylglutarimide (VI). A sample of the 5-substituted isomer (VII) was prepared by the reaction of I with diethyl 2-methyleneglutarate (XVII).10)

Treatment of IV with potassium *tert*-butoxide afforded 3-ethoxycarbonylethylglutarimide (V), which was also obtained by the reaction of VI with sodium ethoxide.

Similarly α,β-unsaturated esters such as ethyl crotonate (IIb), ethyl methacrylate (IIc), and ethyl cinnamate (IId) were allowed to react with I under the same conditions to give 3-

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8) T. Kato, H. Yamanaka, and J. Kawamata, *Chem. Pharm. Bull.* (Tokyo), **17**, 2491 (1969).
9) S.D. Worle and C.R. Hauser, *J. Org. Chem.*, **28**, 725 (1963).
10) M.M. Rauhutt and H. Currier, U.S. Patent 3074999 (1958) [*C.A.*, **58**, 11224 (1960)].

acetyl glutarimide derivatives (IIIb—d), however, none of the products corresponding to IV, V, VI, and VII could be isolated.

Although details of the formation of these products are not clear at present, likely pathways are proposed as follows: Michael addition of IIa to active methylene of I affords ethyl 4-carbamoyl-5-oxo-hexanoate (XVIII) as an intermediate, which cyclizes to 3-acetylglutarimide (IIIa). Further Michael addition of IIa to the α- or γ-carbon of XVIII affords an intermediate XX or XIX, respectively. Whichever is formed then cyclizes to VII or VI, respectively. Deacetylation of XIX gives IV, which cyclizes to V. Compound (V) is also obtaineble by treatment of VI with sodium ethoxide.

In the case of substituted esters (IIb—d), Michael addition of the second molecule of esters (IIb—d) to XVIII′ seems to be difficult, resulting only in the formation of 3-acetylglutarimide derivatives (IIIb—d).

Experimental[11]

Reaction of Acetoacetamide (I) with Ethyl Acrylate (IIa)——1) To an EtONa–EtOH solution prepared from 0.7 g of Na and 50 ml of abs. EtOH, was added 3.5 g of I and 3 g of IIa with stirring. After 10 min, 40 ml of EtOH were added to the reaction mixture, and stirring was continued for a week at room temperature. After neutralizing with 10% HCl, the mixture was condensed *in vacuo*. The residue was extracted with AcOEt, and the AcOEt solution was dried, condensed to give 4.3 g of an oily residue, which was purified by silica gel column chromatography using ether–petroleum benzin (1: 1), and ether as eluants. From the first eluted fraction, a crude crystalline substance was obtained. Purification by distillation gave an oil of bp 130—135° (0.07 mmHg), which solidified to give crystals of mp 88—95° (IIIa). Yield, 1.36 g (29%). Recrystallization from ether gave colorless prisms of mp 95—96° (IIIa), and colorless plates of mp 82—91° (IIIa′). *Anal.* Calcd. for $C_7H_9O_3N$ (IIIa): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.69; H, 5.70; N, 8.74. *Anal.* Calcd. for $C_7H_9O_3N$ (IIIa′): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.27; H, 5.73; N, 8.78. UV $\lambda_{max}^{CHCl_3}$ mμ (log ε): IIIa: 283(3.193), IIIa′: 283(4.058). UV λ_{max}^{EtOH} mμ (log ε): IIIa: 283(3.695), IIIa′: 283(3.699). UV λ_{max}^{Ether} mμ (log ε): IIIa: 275(2.719), IIIa′: 277(4.067). IR ν_{max}^{KBr} cm^{-1}: IIIa (3160, 3060, 1710, 1705, 1685, 1670), IIIa′ (3160, 3080, 1724, 1710, 1685, 1635). NMR ($CDCl_3$) ppm: IIIa: 2.40(3H, s), 1.8—2.9 (4H, m), 3.70 (1H, d, J=7.5 Hz), 8.2—8.9 (1H, b), IIIa′: 2.08 (3H, s), 2.59 (4H, s), 7.8—8.5 (1H, b), 13.58 (1H, s).

The second fraction of ether–petroleum ether eluant was condensed to give a crystalline residue. Recrystallization from petroleum ether gave colorless plates (V), mp 42—43°. Yield, 0.3 g, (7%). *Anal.* Calcd. for $C_{10}H_{15}O_4N$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.66; H, 7.10; N, 6.68. IR ν_{max}^{KBr} cm^{-1}: 3200, 3100, 1725, 1715. NMR ($CDCl_3$) ppm: 1.26 (3H, t, J=7.5 Hz), 1.6—2.9 (9H, m), 4.13 (2H, q, J=7.5 Hz), 8.0—8.6 (1H, b).

From the ether eluted fraction, diethyl 3-carbamoylglutarate (IV) was obtained. Recrystallization from ether and petroleum ether gave colorless needles of mp 65—66°. Yield, 0.35 g (7%). *Anal.* Calcd. for $C_{12}H_{21}O_5N$ (IV): C, 55.58; H, 8.16; N, 5.40. Found: C, 55.92; H, 8.45; N, 5.66. IR ν_{max}^{KBr} cm^{-1}: 3400, 3200, 1720, 1640. NMR ($CDCl_3$) ppm: 1.25 (6H, t, J=7.5 Hz), 1.5—2.1 (4H, m), 2.1—2.6 (5H, m), 4.1 (4H, q, J=7.5 Hz), 5.8—6.2 (1H, b).

2) To a solution of 3.5 g of I in EtONa–EtOH prepared from 0.7 g of Na and 50 ml of abs. EtOH, was added dropwise a solution of 3 g of II in 10 ml of abs. EtOH under reflux over a period of 20 min. The reaction mixture was refluxed for 2 hr with stirring. After neutralizing with 10% HCl, the mixture was evaporated, and extracted with AcOEt. The AcOEt fraction was condensed to give an oily residue, which was purified by silica gel column chromatography using $CHCl_3$ as an eluant, giving 2.9 g (62%) of IIIa as colorless plates of mp 88—95° (from ether).

3) To a solution of 3.5 g of I in *tert*-BuOK–*tert*-BuOH prepared from 1.2 g of K and 50 ml of *tert*-BuOH, was added a solution of 3 g of IIa in 10 ml of *tert*-BuOH within a few min. After the addition was completed, the mixture was refluxed for 1 hr, neutralized with 10% HCl, and condensed under reduced pressure. The residue was extracted with AcOEt. The AcOEt layer was dried, evaporated to give 4.2 g of an oily residue, which was purified by silica gel column chromatography using petroleum benzine–ether (1: 1) and ether as eluants. From the petroleum benzin–ether eluted fraction, colorless needles of mp 75—77° (VII) were obtained. Yield, 0.48 g (10%). *Anal.* Calcd. for $C_{12}H_{17}O_5N$ (VII): C. 56.46; H, 6.71; N, 5.49. Found: C, 56.05; H, 6.53; N, 5.36. IR ν_{max}^{KBr} cm^{-1}: 3160, 1720, 1705, 1625. NMR ($CDCl_3$) ppm: 1.25 (3H, t, J=7.5 Hz), 2.06 (3H, s), 2.3—2.7 (7H, m), 4.1 (2H, q, J=7.5 Hz), 7.5—8.0 (1H, b), 12.45 (1H, s).

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[11] All melting points were uncorrected. Measurements of the NMR spectra were determined on a Hitachi-Perkin Elmer R-20 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded by using a Nippon-bunko IR-S spectrophotometera nd UV spectra with Toshiba-Beckman DB-G type of ultraviolet spectrometer.

From the ether eluted fraction, a crystalline solid was obtained. Recrystallization from ether gave 0.85 g (18%) of IIIa, mp 88—95°. The mother liquor was condensed, and the residue was purified by silica gel chromatography using ether as an eluant to give 0.34 g (4%) of VI, colorless plates of mp 73—74° (petroleum ether–ether). *Anal.* Calcd. for $C_{12}H_{17}O_5N$ (VI): C, 56.46; H, 6.71; N, 5.49. Found: C, 56.70; H, 6.81; N, 5.34. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3240, 1725, 1670. NMR ($CDCl_3$) ppm: 1.24 (3H, t, J=7.5 Hz), 1.65—2.10 (1H, m), 2.27 (3H, s), 2.3 (4H, s). 2.5—2.8 (3H, m), 4.10 (2H, q, J=7.5 Hz), 8.3—8.7 (1H, b).

4) To a solution of 3.5 g of I in *tert*-BuOH–*tert*-BuOH prepared from 1.2 g of K and 40 ml of *tert*-BuOH, was added dropwise a solution of 3 g of IIa in 10 ml of *tert*-BuOH with heating on a steam bath during 20 min. After heating for additional 1 hr, the reaction mixture was neutralized with dil. HCl, and condensed. The residue was extracted with AcOEt. The AcOEt soluble fraction was purified by silica gel chromatography to give 4.1 g of crude IIIa, which was distilled under reduced pressure to give a crystalline substance, bp 130—135° (0.07 mmHg) (IIIa), mp 88—95° (71%).

3-Acetyl-4-methylglutarimide (IIIb)——1) Following the procedure given for the 1st run described above, 3.5 g of I was allowed to react with 3.4 g of ethyl crotonate (IIb) in the presence of EtONa for 3 weeks to give 4.8 g of the product. Recrystallization from ether gave colorless pillars of mp 88—89° (IIIb). Yield, 3.6 g (71%). *Anal.* Calcd. for $C_8H_{11}O_3N$ (IIIb): C, 56.79; H, 6.55; N, 8.28. Found: C, 56.67; H, 6.41; N, 8.45. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 282 (3.711), UV $\lambda_{\max}^{\mathrm{CHCl_3}}$ mμ (log ε): 283 (3.764), UV $\lambda_{\max}^{\mathrm{Ether}}$ mμ (log ε): 278 (3.790).12) IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3160, 3080, 1705, 1685, 1610. NMR ($CDCl_3$) ppm: 1.09 (1.2H, d, J=6 Hz), 1.13 (1.8H, d, J=6 Hz), 2.10 (1.2H, s), 2.48 (1.8H, s), 2.4—3.1 (3.4H, m), 3.4 (0.6H, d, J=7.5 Hz), 8.2—8.9 (1H, b), 13.65 (0.4H, s).13)

3-Acetyl-5-methylglutarimide (IIIc)——1) Following the same procedure as described above, 3.5 g of I was allowed to react with 3.4 g fo of ethyl methacrylate (IIc) in the presence of EtONa for 3 weeks to give 4.4 g of a crude crystalline product. Recrystallization from AcOEt gave colorless needles of mp 116—117° (IIIc). Yield, 3.5 g (69%). *Anal.* Calcd. for $C_8H_{11}O_3N$ (IIIc): C, 56.79; H, 6.55; N, 8.28. Found: C, 57.29; H, 6.78; N, 8.27. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 283 (3.872), UV $\lambda_{\max}^{\mathrm{CHCl_3}}$ mμ (log ε): 283 (4.083), UV $\lambda_{\max}^{\mathrm{Ether}}$ mμ (log ε): 277 (4.060). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3160, 3120, 1710, 1680, 1640, 1615. NMR ($CDCl_3$) ppm: 1.28 (3H, d, J=6.0 Hz), 2.06 (3H, s), 2.2—2.8 (3H, m), 7.8—8.5 (1H, b), 13.55 (1H, s).−14)

3-Acetyl-4-phenylglutarimide (IIId)——Employing the same procedure as described above, 3.5 g of I was allowed to react with 5.3 g of ethyl cinnamate (IId) in the presence of EtONa for 4 weeks to give 7.5 g of a crude product. Recrystallization from EtOH gave colorless needles of mp 166—167° (IIId). Yield, 3.5 g (50%). After removal of IIId, the residue was purified by silica gel chromatography using $CHCl_3$ as an eluant to recover the starting ester IId, 1.8 g (34%). *Anal.* Calcd. for $C_{13}H_{13}O_3N$ (IIId): C, 67.52; H, H, 5.67; N, 6.06. Found: C, 67.85; H, 5.54; N, 6.24. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3160, 1700, 1630, 1610. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 282 (3.830), UV $\lambda_{\max}^{\mathrm{CHCl_3}}$ mμ (log ε): 283 (3.788), UV $\lambda_{\max}^{\mathrm{Ether}}$ mμ (log ε): 278 (3.799).12) NMR ($CDCl_3$+CF_3COOH) ppm: 2.05 (2H, s), 2.24 (1H, s), 2.95—3.15 ($3\frac{1}{3}$H, m), 4.0—4.25 (1H, m), 7.0—7.65 (5H, m), 9.2—9.8 (1H, b).15)

Acetylation of Glutarimide (VIII)——1) To a solution of $LiNH_2$–NH_3 prepared from 0.4 g of Li and 200 ml of liq. NH_3, was added 2.3 g of glutarimide (VIII). After the addition was completed, the mixture was stirred for 1 hr, and 3.2 g of ethyl acetate was added. After stirring for additional 30 min, the reaction mixture was neutralized with 3.2 g of NH_4Cl, and evaporated. To the residue was added ice-water, and the solution was neutralized with 10% HCl, and extracted with AcOEt. The AcOEt soluble layer was dried, condensed to give an oily residue, which was submitted to silica gel chromatography using $CHCl_3$ as an eluant. From the first eluted fraction, 0.15 g of ethylacetoacetate was obtained, and the second fraction was condensed to give a mixture of VIII and IIIa. Repeated recrystallization from ether gave 0.3 g (9.7%) of 3-acetyglutarimide (IIIa), mp 88—95°, and 0.9 g of the mixture of VIII and IIIa.

2) To a solution of $LiNH_2$–NH_3 prepared from 0.28 g of Li and 200 ml of liq. NH_3, was added 0.28 g of VIII. The mixture was stirred for 30 min, and NH_3 was evaporated. After allowing to stand in a desiccator overnight, the residue was suspended in 60 ml of tetrahydrofuran, and 1.57 g of acetyl chloride was added to it. The reaction mixture was stirred for 6 hr and then CO_2 was bubbled into the mixture. After diluting with ice-water followed by neutralization with 10% HCl, the mixture was extracted with AcOEt. The AcOEt soluble fraction was condensed, and purified by silica gel chromatography using $CHCl_3$ as an eluant to give 0.83 g (27%) of IX, colorless needles of mp 69—71° (ether–petroleum ether). The second fraction gave the starting glutarimide (VIII), 0.5 g (22%). *Anal.* Calcd. for $C_7H_9O_3N$ (IX): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.22; H, 5.84; N, 9.15. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3400, 1780, 1705, 1685. NMR ($CDCl_3$) ppm: 1.7—2.25 (2H, m), 2.43 (3H, s), 2.65 (4H, t, J=6.0 Hz).

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12) From UV spectral data, IIIb (and IIId) existed in the mixture of keto and enol form, which however, could not be isolated.

13) The keto-enol ratio of IIIb was about 3: 2.

14) From NMR and UV spectra data, IIIc existed only in the enol form.

15) The keto enol ratio of IIId was about 1: 2.

3-Ethoxycarbonylethylglutarimide (V)——1) To a solution of *tert*-BuOK–*tert*-BuOH prepared from 0.02g of K and 5 ml of *tert*-BuOH, was added 0.13 g of diethyl 4-carbamoylglutarate (IV). After heating for 20 min, the mixture was neutralized with 10% HCl and condensed. The residue was extracted with AcOEt. From the AcOEt soluble fraction, colorless prisms of mp 42—43° (V) (from ether—petroleum ether) were obtained. Yield, 0.06 g (56%).

2) To a solution of EtONa–EtOH prepared from 0.04 g of Na and 5 ml of abs. EtOH, was added 0.2 g of 3-acetyl-3-ethoxycarbonylethylglutarimide (VI). After stirring for 1 day at room temperature, the reaction mixture was neutralized with 10% HCl, and condensed. The resulting residue was extracted with $CHCl_3$, and the $CHCl_3$ layer was condensed to give an oily residue, which was purified by silica gel chromatography using ether–petroleum ether (4: 1) as an eluant to give 0.7 g (42%) of V, mp 42—43°.

Hydrolysis of IIIa——1) The mixture of 0.7 g of IIIa and 5 ml of conc. HCl was heated for 1 hr, during which time CO_2 gas envolved was identified by passing into a $Ba(OH)_2$ solution. The reaction mixture was evaporated *in vacuo*, and the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract was purified by vacuum distilation to give 0.45 g (77%) of colorless oil, bp 104—108° (0.4 mmHg) (X) (lit.[5] bp 180° (20 mmHg)). *Anal.* Calcd. for $C_6H_{10}O_3$ (X): C, 55.35; H, 7.75. Found: C, 54.98; H, 7.75. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—3000, 1705. NMR ($CDCl_3$) ppm: 2.15 (3H, s), 1.7—2.7 (6H, m), 7.45 (1H, broad s).

2) A solution of 0.5 g of IIIa in 4 ml of 5% KOH was allowed to stand for a day at room temperature. After neutralizing with dil. HCl, the mixture was condensed. The resulting residue was extracted with AcOEt. From the AcOEt extract, colorless prisms of mp 117—118° (MeOH–ether) were obtained. Yield, 0.14 g (42%). *Anal.* Calcd. for $C_7H_{11}O_4N$ (XI); C, 48.55; H, 6.40; N, 8.09. Found: C, 48.35; H, 6.33; N, 8.11. IR ν_{max}^{KBr} cm^{-1}: 3420, 3180, 1710—1690, 1650, 1630. NMR ($CDCl_3$–CF_3COOH) ppm: 2.36 (3H, s), 1.9—2.7 (4H, m), 3.64 (1H, t, 6.8 Hz), 6.6—7.8 (1H, b).

3) A solution of 0.5 g of IIIa in 4 ml of 50% KOH was allowed to stand at room temperature for a day. After acidifying with conc. HCl, the solution was condensed *in vacuo*. The residue was extracted with hot ether. The ether extract was purified by recrystallization from $CHCl_3$ to give colorless needles of mp 96—97° (lit.[6] mp 97—98°), undepressed on admixture with a sample of glutaric acid (XII).[6] Yield, 0.18 g (45%).

3-Acetoxyethylideneglutarimide (XIII)——To a solution of 0.78 g of IIIa in 10 ml of pyridine, was added 0.4 g of acetyl chloride with ice-cooling. After allowing to stand at room temperature overnight, the reaction mixture was condensed under reduced pressure. The residue was added to H_2O, and extracted with AcOEt. The AcOEt solution was condensed to give a crystalline substance, which was purified by recrystallization from ether to afford colorless prisms of mp 125—128°, undepressed on admixture with an authentic sample of XIII.[8] Yield, 0.6 g (61%).

Ammonolysis of IIIa——1) A solution of 0.5 g of IIIa and 0.2 g of NH_4NO_3 in 20 ml of abs. EtOH saturated with NH_3 gas was placed in a sealed glass tube, and heated at 65° for 6 hr. After evaporating, the reaction mixture was extracted with AcOEt. The AcOEt extract was purified by crystallization from MeOH to give colorless needles (XVI) of mp 234—235° (decomp.), whose IR spectrum was identical in every respect with that of the authentic sample of XVI.[7] Yield, 0.3 g (59%).

2) A mixture of 0.5 g of IIIa and 10 ml of 28% NH_4OH was allowed to stand at room temperature. After 2 days, the mixture was evaporated to dryness. The residual solid was purified by recrystallization from MeOH to give colorless needles of mp 167—168° (XV). Yield, 0.25 g (45%). *Anal.* Calcd. for $C_7H_{12}O_3N_2$ (XV): C, 48.83; H, 7.03; N, 16.27. Found: C, 48.75; H, 7.12; N, 16.64. IR ν_{max}^{KBr} cm^{-1}: 3300, 3120, 1705, 1660, 1620. NMR ($CDCl_3$–CF_3COOH) ppm: 2.28 (3H, s), 2.64 (4H, s), 8.5—9.0 (1H).

The filtrate, after removal of XV by recrystallization, was condensed, and the residue was recrystallized from MeOH–AcOEt to give colorless needles of mp 241—242° (decomp.) (XVI), undepressed on admixture with an authentic sample of XVI.[8] Yield, 0.1 g (20%).

3-Acetyl-3-ethoxycarbonylethylglutarimide (VI)——To a solution of EtONa–EtOH prepared from 0.08 g of Na and 10 ml of abs. EtOH, was added 0.5 g of IIIa and 0.58 g of ethyl 3-bromopropionate. After heating for 4 hr, the reaction mixture was neutralized with 10% HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by silica gel chromatography using ether–petroleum ether (1: 4) and then ether as eluants. From the ether–petroleum ether fraction, 0.1 g (20%) of IIIa was recovered. The ether eluted fraction gave colorless needles of mp 73—74°, undepressed on admixture with a sample (VI) obtained in above run. Yield, 0.25 g (31%).

3-Acetyl-5-ethoxycarbonylethylglutarimide (VII)——To a solution of EtONa–EtOH prepared from 0.06 g of Na and 20 ml of abs. EtOH, was added 0.3 g of I. The mixture was then heated, and a solution of 0.5 g of diethyl 2-methylene glutarate (XVII)[10] in 5 ml of abs. EtOH was added slowly during 20 min. After refluxing for 3 hr, the reaction mixture was neutralized with 10% HCl, and condensed. The resulting residue was extracted with AcOEt. The AcOEt extract was purified by silica gel chromatography using ether as an eluant to give crystals. Recrystallization from ether–petroleum ether afforded colorless needles of mp 72—74°, undepressed on admixture with a sample of VII obtained previously. Yield, 0.13 g (22%).

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