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Reaction of β -aminocrotonamide (**1**) with succinic anhydride gave β -succinamidocrotonamide (**3a**), which was treated with base to cyclize to 3,4-dihydro-6-methyl-4-oxo-2-pyrimidinepropanoic acid (**4a**). Similarly, pyrimidinepentanoic acid derivative **4b** was prepared from compound **1** and glutaric anhydride. Reaction of compound **1** with dimethyl succinate in the presence of sodium methoxide gave the pyrimidine derivative **4a**. Similar reaction of compound **1** with glutarate, adipate, and phthalate gave the corresponding pyrimidines **4b**, **4c** and **4d**, while reaction of compound **1** with malonate gave 2-hydroxypyridine derivative **11** and dimethylpyrimidinone **4e**. Reaction of dimethyl fumarate with compound **1** in the presence of methoxide gave a poor yield of pyrrolo[3,4-c]pyridine derivative **13**.

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Previously, we have reported that the reaction of β -aminocrotonamide (**1**) with acetylating reagents such as acetic anhydride and acetyl chloride gives β -acetamidocrotonamide, which, on treatment with base, cyclizes to 2,6-dimethyl-4-pyrimidinone (**1a-c**). Reaction of the amide **1** with esters such as ethyl acetate under the basic condition gave the same pyrimidinone, directly (**1d**). In order to examine the generality of these reactions in more detail, we investigated the reaction of the amide **1** with dibasic acid anhydrides and dibasic acid esters, which is the subject of the present paper.

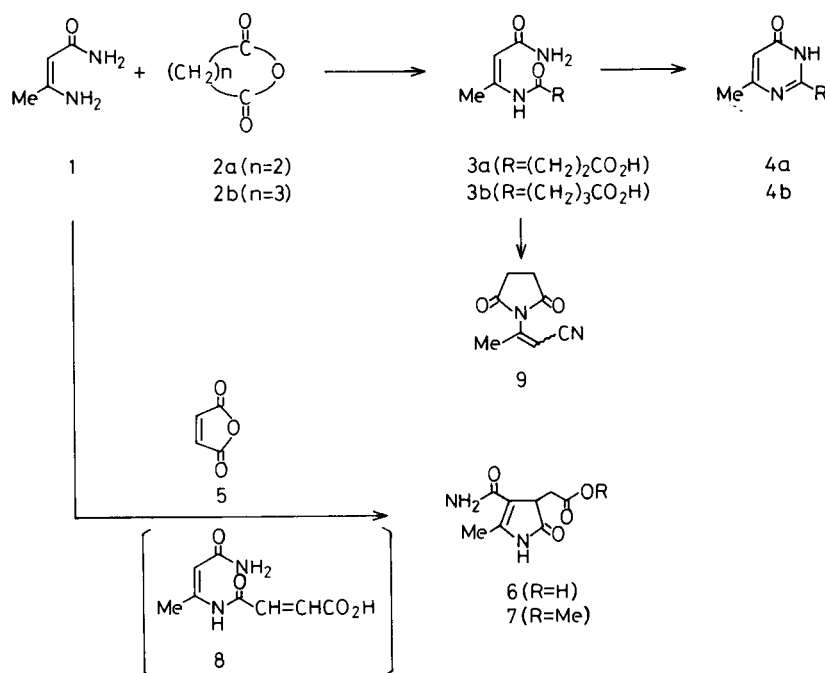
When β -aminocrotonamide (**1**) was allowed to react with succinic anhydride (**2a**), β -succinamidocrotonamide (**3a**) was obtained in 38% yield. Similarly, reaction of **1** with glutaric anhydride (**2b**) gave rise to β -glutamamidocrotonamide (**3b**) in 48% yield.

Reaction of **1** with maleic anhydride (**5**) under the same condition afforded 4-carbamoyl-2,3-dihydro-5-methyl-2-oxo-1*H*-pyrrole-3-acetic acid (**6**). Structural assignment was made on the basis of elemental analyses and spectral data detailed in the experimental section. Treatment of **6** with diazomethane gave the methyl ester **7**. In this reaction, the *N*-acylated adduct **8** would be a reasonable intermediate, which, on intramolecular Michael addition, cyclizes to the product **6** (**2**).

Reaction of **1** with phthalic anhydride resulted in the formation of a resinous substance, from which the acylated compound could not be isolated.

Next, cyclization of **3** to the pyrimidinone **4** was investigated. Thus, treatment of **3a** with sodium methoxide in methanol gave the pyrimidinone **4a** ($R = (\text{CH}_2)_2\text{CO}_2\text{H}$) in 66% yield. Similarly, **3b** cyclized under the same condi-

Scheme 1



tion to give the pyrimidinone **4b** in 65% yield. Heating of **3a** and **3b** in aqueous sodium hydroxide (10%) gave the corresponding pyrimidinones, **4a** and **4b**, in lower yields.

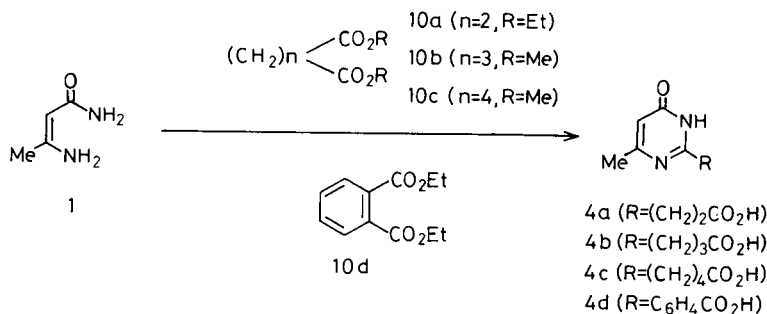
Heating of **3a** in tetralin under reflux also gave the pyrimidinone **4a** in very poor yield, while heating of **3a** in acetic anhydride under reflux gave rise to β -succinimido-crotononitrile (**9**) in 20% yield. The β -acylamido structure of **3a** is given consistently by the formation of the succinimide derivative **9** as well as spectral data shown in experimental section.

Heating of a mixture of **1** and diethyl succinate (**10a**, $n = 2$, $R = Et$) without solvent gave a resinous product. However, refluxing of the mixture of ethanol in the presence of sodium ethoxide gave the pyrimidinone **4a** directly in 46% yield. Dimethyl glutarate (**10b**, $n = 3$, $R = Me$), dimethyl adipate (**10c**, $n = 4$, $R = Me$) and diethyl phthalate (**10d**) were also allowed to react with **1** under the similar condition to give the corresponding pyrimidinones, **4b**, **4c**, and **4d**, respectively.

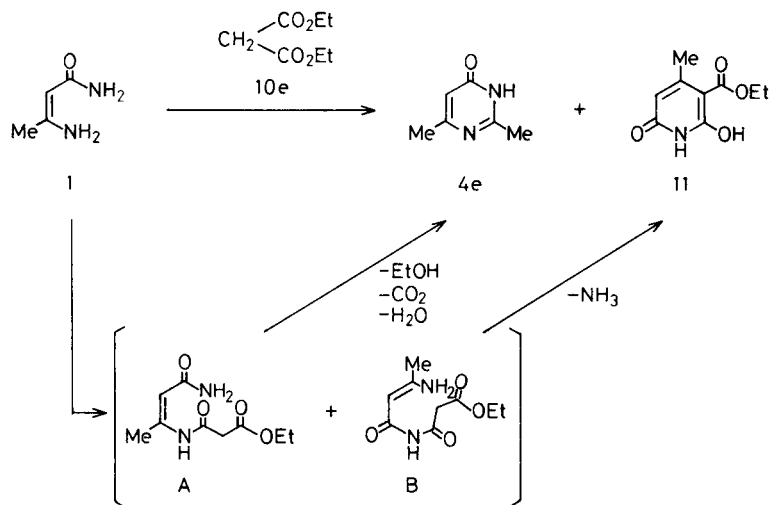
Attempts to prepare the pyrimidinone (**4**, $R = CO_2H$) by the reaction of diethyl oxalate with **1** under the same condition failed. It is of interest to note that the reaction of diethyl malonate (**10e**) with **1** gave the 2,6-dimethyl-4(3*H*)-pyrimidinone (**4e**) and 2-hydroxypyridine **11**. The formation of the pyrimidinone **4e** can be explained by the usual manner as described before for **1d**, that is, the first stage of the reaction would be the acylation of the β -amino group giving intermediate **A**, which, on cyclization accompanied with hydrolysis and decarboxylation, is converted to the pyrimidinone **4e**. On the other hand, formation of the 2-hydroxypyridine derivative **11** can be elucidated as follows: the ester **10e** would react with the amide nitrogen of **1** to give the imide intermediate **B**, from which ammonia eliminates to afford the 2-hydroxypyridine **11**.

Lastly, reaction of **1** with dimethyl fumarate and maleate was carried out. Thus, treatment of **1** with dimethyl fumarate (**12**) in methanol in the presence of sodium methoxide gave 4-methyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-(2*H*,

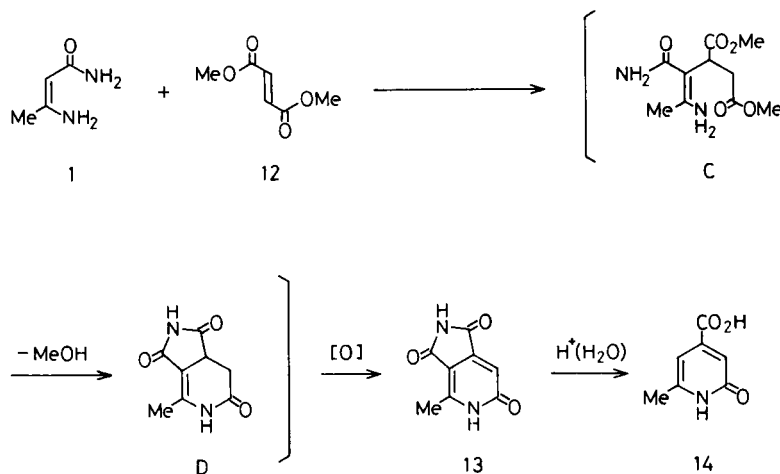
Scheme 2



Scheme 3



Scheme 4



5*H*)-trione (**13**) in 17% yield. Similar treatment of **1** with dimethyl maleate gave a resinous substance, from which none of crystalline product was isolated. As detailed in the experimental section, elemental analyses and spectral data are consistent with the structure **13**. Hydrolysis of **13** with hydrochloric acid gave 1,2-dihydro-6-methyl-2-oxo-4-pyridinecarboxylic acid (**14**). A likely mechanism of the formation of the product **13** can be proposed as follows; Michael addition of dimethyl fumarate with the crotonamide **1** would give the adduct **C**. Next stage involves cyclization to give the intermediate **D**, which is oxidized to give the product **13**.

In conclusion, with the amide **1**, saturated diacid anhydrides and esters react in the similar manner to that of corresponding monoacid derivatives giving 2-carboxyalkylpyrimidine derivatives (**4**), while unsaturated diacid derivatives react in a different manner to give the pyrrole derivative (**6**) and the pyridine derivative (**13**). Though the literature contains several references (5a-c) to synthesize 2-carboxyalkylpyrimidine derivatives, our method would give more satisfactory results.

EXPERIMENTAL

All melting points are uncorrected. Infrared (ir) spectra were taken on a JASCO IR-S spectrometer or a JASCO A-102 spectrometer. Nuclear magnetic resonance (nmr) spectra were taken at 60 MHz with a Hitachi R-20 spectrometer or a JEOL JNM-PMX 60 spectrometer. As an internal standard, tetramethylsilane in deuteriochloroform or sodium 2,2-dimethyl-2-silapentane-5-sulfonate in dimethylsulfoxide-*d*₆ was used. Chemical shifts are expressed in ppm from an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad.

β -Succinamidocrotonamide (**3a**).

A mixture of β -aminocrotonamide (**1**) (5 g, 0.05 mole) and succinic anhydride (**2a**) (10 g, 0.10 mole) in chloroform (100 ml) was refluxed for 3 hours. After cooling, separated crystals were collected by suction and

then washed with methanol. Recrystallization from methanol gave 3.83 g (38%) of the product **3a** as colorless needles, mp 159-160°; ir (Nujol): 3320, 3250, 3120, 2730-2450, 1713, 1694, 1637, 1620 cm⁻¹; ¹H-nmr (dimethylsulfoxide-*d*₆): δ 2.23 (s, Me, 3H), 2.50 (s, (CH₂)₂, 4H), 4.93 (s, =CH, 1H), 6.5-7.6 (br, NH₂, 2H), 11.0-12.7 (br, NH and OH, 2H).

Anal. Calcd. for C₈H₁₂N₂O₄: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.83; H, 6.02; N, 14.12.

β -Glutamamidocrotonamide (**3b**).

Following the same procedure described above, compound **1** (5 g, 0.05 mole) was treated with glutaric anhydride (**2b**) (11.4 g, 0.10 mole) to give 5.14 g (48%) of the product **3b** as colorless needles (from methanol), mp 150-151°; ir (Nujol): 3370, 3270, 3170, 2720-2520, 1700, 1655, 1630, 1600 cm⁻¹; ¹H-nmr (dimethylsulfoxide-*d*₆): δ 2.25 (s, Me, 3H), 1.45-2.70 (m, (CH₂)₃, 6H), 4.95 (s, =CH, 1H), 6.5-7.7 (br, NH₂, 2H), 10.8-13.0 (br, NH and OH, 2H).

Anal. Calcd. for C₉H₁₄N₂O₄: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.56; H, 6.72; N, 12.95.

4-Carbamoyl-2,3-dihydro-5-methyl-2-oxo-1*H*-pyrrole-3-acetic Acid (**6**).

Maleic anhydride (**5**) (3.9 g, 0.04 mole) was added to a solution of compound **1** (2 g, 0.02 mole) in chloroform (40 ml). A slightly exothermic reaction took place immediately to give precipitates. The mixture was refluxed for 2.5 hours. Crystals separated were collected by suction, and then washed with acetone and water successively. Insoluble crystals were purified by recrystallization from methanol to give 0.58 g (16%) of the product **6** as colorless needles, mp 190-191°; ir (Nujol): 3390, 3270, 3160, 2800-2400, 1710, 1670, 1645, 1595 cm⁻¹; ¹H-nmr (dimethylsulfoxide-*d*₆): δ 2.08 (s, Me, 3H), 2.56 (d, CH₃, 2H, J = 4 Hz), 3.56 (t, CH, 1H, J = 4 Hz), 7.3-7.8 (br, NH₂, 2H), 9.1-9.8 (br, NH, 1H).

Anal. Calcd. for C₈H₁₀N₂O₄: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.31; H, 5.05; N, 14.17.

Methyl 4-Carbamoyl-2,3-dihydro-5-methyl-2-oxo-1*H*-pyrrole-3-acetate (**7**).

Compound **6** (0.1 g, 0.5 mmole) was dissolved in warm dioxane (40 ml). A solution of excess diazomethane in ether was added to this solution at room temperature and the mixture was stirred for 30 minutes. The solvent was evaporated *in vacuo*. The resulting residue was recrystallized from acetone to give 0.10 g (94%) of the product **7** as colorless needles, mp 200-202°; ir (Nujol): 3310, 3140, 1720, 1690, 1663, 1640, 1605 cm⁻¹; ¹H-nmr (dimethylsulfoxide-*d*₆): δ 2.05 (s, Me, 3H), 2.58 (d, CH₂, 2H, J = 4 Hz), 3.60 (s, OMe and CH, 4H), 6.8-7.3 (br, NH₂, 2H), 9.2-9.6 (br, NH, 1H).

Anal. Calcd. for C₉H₁₂N₂O₄: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.64; H, 5.68; N, 12.93.

3,4-Dihydro-6-methyl-4-oxo-2-pyrimidinepropanoic Acid (**4a**).

A.

Compound **3a** (1 g, 0.005 mole) was added to a sodium methoxide solution in methanol prepared from sodium metal (0.64 g, 0.028 g atom) and absolute methanol (10 ml). After refluxing for 5 hours, the reaction mixture was condensed to dryness *in vacuo*. The residue was dissolved in a small amount of water (*ca.* 10 ml), and the solution was acidified (pH 3.5) with concentrated hydrochloric acid under ice-water cooling. The mixture was condensed to dryness *in vacuo*, and the residue was extracted with hot absolute ethanol. The ethanol soluble fraction gave 0.6 g (66%) of the product **4a** as colorless needles (from ethanol), mp 193-194° dec; ir (potassium bromide): 3055, 2955, 2650-2400, 1710, 1655, 1600 cm⁻¹; ¹H-nmr (dimethylsulfoxide-d₆): δ 2.15 (s, Me, 3H), 2.72 (s, (CH₂)₂, 4H), 6.05 (s, =CH, 1H), 11.5-12.9 (br, NH and OH, 2H).

Anal. Calcd. for C₈H₁₀N₂O₃: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.75; H, 5.45; N, 15.16.

B.

A solution of **3a** (1 g, 0.005 mole) in 10% aqueous sodium hydroxide (6 ml) was refluxed for 5 hours. The solution was acidified (pH 3.5) with concentrated hydrochloric acid and the mixture was condensed to dryness *in vacuo*. Extraction with ethanol gave 0.4 g (44%) of the product **4a**.

C.

Compound **1** (1 g, 0.01 mole) and ethyl succinate (**10a**) (3.48 g, 0.02 mole) were added to a sodium ethoxide solution in ethanol prepared from sodium metal (1.15 g, 0.05 g atom) and absolute ethanol (20 ml). The mixture was refluxed for 1.5 hours. The solution was condensed *in vacuo* and the residue was dissolved in a small amount of water. The solution was acidified (pH 3.5) with concentrated hydrochloric acid. The solution was condensed to dryness *in vacuo* and the residue was extracted with hot acetone and then with absolute ethanol. The ethanol soluble fraction gave 0.84 g (46%) of the product **4a**.

β-Succinimidocrotonitrile (**9**).

A solution of **3a** (0.5 g, 0.0025 mole) in acetic anhydride (5 ml) was refluxed for 2 hours. The reaction mixture was condensed *in vacuo* to give an oily residue, to which water was added. The mixture was warmed on a water bath for 30 minutes and then condensed to dryness *in vacuo*. The residue (0.5 g) was chromatographed on a silica gel (10 g) column using chloroform as an eluant. Crystalline substance thus obtained was recrystallized from ether to give 0.08 g (20%) of the product **9** as colorless needles, mp 108-109°; ir (chloroform): 2230, 1790, 1730, 1645 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 2.18 (s, Me, 3H), 2.85 (s, (CH₂)₂, 4H), 5.59 (s, =CH, 1H).

Anal. Calcd. for C₈H₈N₂O₂: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.53; H, 4.85; N, 17.06.

3,4-Dihydro-6-methyl-4-oxo-2-pyrimidinebutanoic Acid (**4b**).

A.

Following the procedure A given for compound **4a**, compound **3b** (1.1 g, 0.005 mole) was treated with sodium methoxide to give 0.64 g (65%) of the product **4b** as colorless needles (from ethanol), mp 191-192.5°; ir (potassium bromide): 2930, 2655-2400, 1700, 1655, 1595 cm⁻¹; ¹H-nmr (dimethylsulfoxide-d₆): δ 2.20 (s, Me, 3H), 1.8-2.9 (m, (CH₂)₃, 6H), 6.10 (s, =CH, 1H), 10.8-12.8 (br, NH and OH, 2H).

Anal. Calcd. for C₉H₁₂N₂O₃: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.10; H, 6.24; N, 14.30.

B.

Following the procedure B given for compound **4a**, compound **3b** was treated with 10% aqueous sodium hydroxide to give 0.4 g (40%) of the product **4b**.

C.

Following the procedure C given for compound **4a**, compound **1** (1 g,

0.01 mole) was allowed to react with dimethyl glutarate (**10b**) (3.2 g, 0.02 mole) in a sodium methoxide-methanol solution prepared from sodium metal (1.15 g, 0.05 g atom) and absolute methanol (20 ml). Similar work-up described above gave the product **4b**, 0.71 g (36%).

3,4-Dihydro-6-methyl-4-oxo-2-pyrimidinepentanoic Acid (**4c**).

Following the procedure C given for compound **4a**, compound **1** (1 g, 0.01 mole) was allowed to react with dimethyl adipate (**10c**) (3.48 g, 0.02 mole). After acidification followed by evaporation *in vacuo*, the resulting residue was extracted with hot absolute ethanol. The ethanol solution was condensed *in vacuo* and the residue was extracted with hot acetone. The acetone soluble fraction gave 1.1 g (52%) of the product **4c** as colorless needles (from acetone), mp 207-209°; ir (potassium bromide): 2935, 1720, 1655, 1605 cm⁻¹; ¹H-nmr (dimethylsulfoxide-d₆): δ 1.3-2.0 (m, CH₂CH₂CH₂CH₂, 4H), 2.15 (s, Me, 3H), 2.2-2.8 (m, CH₂CH₂CH₂CH₂, 4H), 6.03 (s, =CH, 1H), 11.3-12.8 (br, NH and OH, 2H).

2-(3,4-Dihydro-6-methyl-4-oxopyrimidin-2-yl)benzoic Acid (**4d**).

Following the procedure C given for compound **4a**, compound **1** (1 g, 0.01 mole) was allowed to react with diethyl phthalate (**10d**) (4.44 g, 0.02 mole). The reaction mixture was cooled. Separated crystals were collected by suction, and dissolved in water. The solution was acidified (pH 3.5) with concentrated hydrochloric acid, and separate crystals were collected. Recrystallization from ethanol gave 0.4 g (17%) of the product **4d** as colorless needles, mp 201-202°; ir (potassium bromide): 3200, 3100-2700, 2680-2380, 1690, 1650, 1600, 1585, 1485 cm⁻¹; ¹H-nmr (dimethylsulfoxide-d₆): δ 2.20 (s, Me, 3H), 6.20 (s, =CH, 1H), 7.4-7.9 (m, benzene ring H, 4H).

Anal. Calcd. for C₁₂H₁₀N₂O₃: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.53; H, 4.42; N, 11.92.

Reaction of **1** with Diethyl Malonate.

According to the procedure C given for compound **4a**, compound **1** (1 g, 0.01 mole) was allowed to react with diethyl malonate (**10e**) (3.2 g, 0.02 mole). The reaction mixture was acidified (pH 6.5) with concentrated hydrochloric acid and crystals separated were collected by suction. The filtrate was condensed to dryness *in vacuo*. The residue was extracted with chloroform. The organic layer was condensed *in vacuo* and the residue was purified by chromatography on a silica gel column. Elution with 3% methanol in chloroform gave 0.08 g (6%) of 2,6-dimethyl-4(3H)-pyrimidinone (**4e**) as colorless needles (from ethyl acetate), mp 191-192° (lit (1a) mp 195-195.5°), undepressed on admixture with an authentic sample prepared according to the literature. The above crystals were suspended in water. The suspension was acidified (pH 4.5) with 10% hydrochloric acid, and the mixture was allowed to stand in an ice bath and separated crystals were collected by suction. Recrystallization from ethanol gave 0.2 g (10%) of ethyl 1,6-dihydro-2-hydroxy-4-methyl-6-oxo-3-pyridinecarboxylate (**11**) as yellow needles, mp 214-215° (lit (3) mp 218°). The ir spectrum of the product **11** was identical in every respect with that of an authentic sample prepared according to the literature (3).

4-Methyl-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione (**13**).

According to the procedure C given for compound **4a**, compound **1** (1 g, 0.01 mole) was allowed to react with dimethyl fumarate (**12**) (2.88 g, 0.02 mole). The mixture was evaporated *in vacuo*, and the residue was acidified (pH 3.5) with concentrated hydrochloric acid. The acidic solution was allowed to stand in an ice bath and separated crystals were filtered. Recrystallization from water gave 0.29 g (17%) of the product **13** as brown needles, mp 321-323° dec; ir (potassium bromide): 3230, 3105, 2975, 1760, 1720, 1635, 1600 cm⁻¹; ¹H-nmr (dimethylsulfoxide-d₆): δ 2.51 (s, Me, 3H), 6.53 (s, =CH, 1H), 11.0-12.8 (br, 2 × NH, 2H).

Anal. Calcd. for C₈H₆N₂O₃: C, 53.93; H, 3.40; N, 15.73. Found: C, 53.74; H, 3.31; N, 15.50.

Acidic Hydrolysis of **13**.

A solution of **13** (0.18 g, 1 mmole) in 10% hydrochloric acid (10 ml) was

refluxed for 15 hours. The solution was condensed *in vacuo* to give a crystalline residue, which was collected by suction and purified by recrystallization from water to give 0.11 g (69%) of 1,2-dihydro-6-methyl-2-oxo-4-pyridinecarboxylic acid (**14**) as brown needles, mp 300° dec (lit (4) mp 314°). Its ir spectrum was identical in every respect with that of an authentic sample prepared according to the literature (4).

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REFERENCES

- (1a) T. Kato, H. Yamanaka, and T. Shibata, *Yakugaku Zasshi*, **87**, 955 (1967); (b) T. Kato, H. Yamanaka, and J. Kawamata, *ibid.*, **89**, 460 (1969); (c) T. Kato, H. Yamanaka, and J. Kawamata, *Chem. Pharm. Bull.*, **17**, 2411 (1969); (d) T. Kato, H. Yamanaka, and S. Konno, *Yakugaku Zasshi*, **90**, 509 (1960).
- (2) T. Kato, *Yuki Gosei Kagaku Kyokai Shi*, **32**, 632 (1974).
- (3) H. Rogerson, J. F. Thorpe, and J. Field, *J. Chem. Soc.*, **87**, 1687 (1905).
- (4) J. C. Bardhan, *J. Chem. Soc.*, 2227 (1929).
- (5a) R. G. Jones, E. C. Kornfeld, and K. C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 3539 (1950); (b) H. Arai, W. K. Hagmann, H. Suguna, and S. M. Hecht, *J. Am. Chem. Soc.*, **102**, 6631 (1980); (c) W. K. Hagmann, F. Z. Basha, M. Hashimoto, R. B. Frye, S. Kojo, and S. M. Hecht, *J. Org. Chem.*, **46**, 1413 (1981).