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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XI.[1] Reaction of 1-Methyl-2(1*H*)-pyridone Derivatives with Formaldehyde and Hydrochloric Acid

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Reaction of 1-methyl-2(1*H*)-pyridone with formaldehyde and hydrochloric acid was carried out. The products proved in this reaction were 5-hydroxymethyl-1-methyl-2(1*H*)-pyridone (III) in 46% yield from 1-methyl-2(1*H*)-pyridone (I), 5-ethyl-3-hydroxymethyl-1-methyl-2(1*H*)-pyridone (VIII) from 5-ethyl-1-methyl-2(1*H*)-pyridone (VII), and 6-hydroxymethyl-1-methyl-2(1*H*)-quinolone (IX) from 1-methyl-2(1*H*)-quinolone (II).

1-Methyl-2(1*H*)-pyridone (I) is prepared from pyridine in two steps[3] and can be reverted to pyridine.[4] Nitration of I has been reported to occur easily in 3- and/or 5-position, and an electrophilic substitution is expected to occur in positions different from that in pyridine 1-oxide. From these points, various reactions carried out on I would offer a new synthetic route to pyridine derivatives and would be of interest in organic chemistry.

The fact that 1-methyl-2(1*H*)-quinolone (II) has a specific relation to quinoline has been reported in Part IX of this series.[5] In the present series of work, reaction of I and II with formaldehyde and hydrochloric acid was carried out and some new observations on this reaction are described herein.

A mixture of 10 g of I, 6 g of paraformaldehyde, and 30 ml of conc. hydrochloric acid was stirred with heating in an oil bath of 100° for 3 hr, 60 g of sodium acetate and 12 g of acetic anhydride were added, and the mixture was further stirred at 100° for 3 hr. Sodium acetate was filtered off from the reaction mixture and the mixture was extracted with isoamyl alcohol. The extract was dried, isoamyl alcohol was evaporated, and the residue was extracted with chloroform to remove inorganic substances. The chloroform layer was passed through a chromatographic column over alumina and 5.9 g of colorless needles (III), mp 106—108°, $C_7H_9O_2N$, was obtained in 46% yield.

The analytical values of III corresponds to I with introduction of one hydroxymethyl group and its infrared (IR) spectrum (in Nujol) exhibited absorption for O–H at 3280 cm^{-1}, amide C=O at 1665 cm^{-1}, C–O at 1025 cm^{-1}, lone H in the aromatic ring at 910 cm^{-1}, and adjacent two H in the aromatic ring at 849 cm^{-1}.

From these spectral data, substitution seems to have occured at 4- or 5-position. The nuclear magnetic resonance (NMR) spectrum (Fig. 1) of III (in $CDCl_3$) showed signals at 3.45 ppm (3H, singlet, N–CH_3), 4.40 ppm (3H, singlet, CH_2OH), 6.45 ppm (1H, quartet, J=9, 1.5 cps), and a peak for 2H at around 7.38 ppm. According to the reported data of Jackman and Elvidge,[6] on the NMR spectrum of I (in $CDCl_3$), the signal at 6.57 ppm has been assigned to the 3-proton, that at 7.26 ppm to 4-proton, that at 6.15 to 5-proton, and

1) Part X: H. Tomisawa and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 923 (1970).
2) Location: *Nankozawa, Odawara, Sendai.*
3) E.A. Prill and S.M. McElvain, "Organic Syntheses"., Collected Vol. II, 1943, p. 419.
4) O. Fischer and M. Chur, *J. pract. Chem.*, [2] **93**, 363 (1916); A.H. Berrie, G.T. Newhold, and F.S. Spring, *J. Chem. Soc.*, **1951**, 2590.
5) H. Tomisawa, M. Watanabe, R. Fujita, and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 917 (1970).
6) L.M. Jackman and J.A. Elvidge, *J. Chem. Soc.*, **1961**, 853.

that at 7.31 to 6-proton. By reference to these data, the peak at 6.45 ppm would be the proton at 3- or 5-position, and there would be an adjacent proton from the coupling constant of 9 cps, and further, this proton would be in *para* position from the coupling constant of 1.5 cps. The peak at around 7.38 ppm would be assigned to the protons at 4- and 6-positions. From these NMR spectral data, III would be formulated as 5-hydroxymethyl-1-methyl-2(1*H*)-pyridone and this formulation would not be inconsistent the IR spectrum.

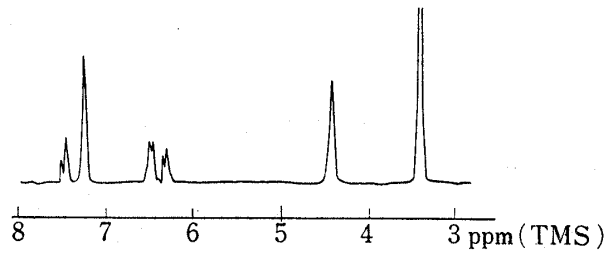

Fig. 1. NMR Spectrum of III in $CDCl_3$ (60 Mcps)

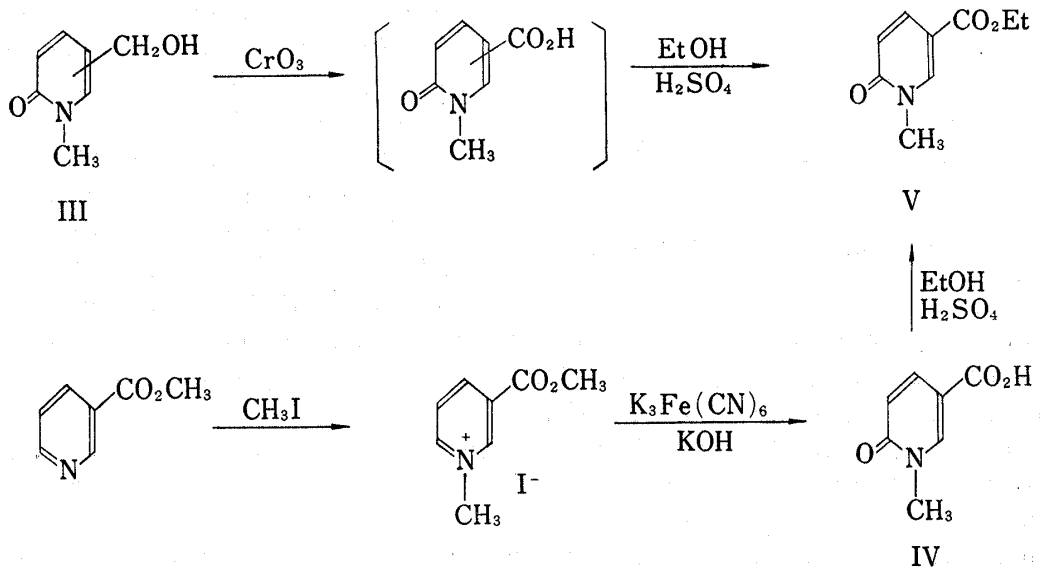

Chart 1

In order to confirm the structure of III, the reactions shown in Chart 1 were carried out. Oxidation of III with chromium trioxide followed by esterification afforded a product which was identified by mixed melting point determination and IR spectral comparison with 5-ethoxycarbonyl-1-methyl-2(1*H*)-pyridone (V), derived from 5-carboxy-1-methyl-2(1*H*)-pyridone (IV), whose structure has been chemically proved by Sugasawa, *et al.*[7] Consequently, III is definitely 5-hydroxymethyl-1-methyl-2(1*H*)-pyridone.

The foregoing reaction conditions gave the highest yield of the product. The reaction did not progress at room temperature and the starting compound was recovered. Even if reacted at 100°, longer time of the reaction resulted in the formation of a resinous substance considered to be a polymer. Addition of sodium acetate and acetic anhydride to the reaction mixture in order to obtain the acetoxymethyl compound failed to reveal the presence of any product other than the hydroxymethyl derivative. After-treatment with potassium carbonate, in an attempt to obtain the hydroxymethyl compound, gave III in only 20% yield.

These experimental results seem to support the assumption that the acetoxymethyl compound is extracted by the organic solvent but is so unstable that it converts into the hydroxymethyl compound. However, 5-acetoxymethyl-1-methyl-2(1*H*)-pyridone (VI), mp 45—47°, obtained by acetylation of III with acetic anhydride, is comparatively stable in 10% acetic acid and is not hydrolyzed to III. Consequently, the above-mentioned reaction con-

7) S. Sugasawa and T. Okayama, *Yakugaku Zasshi*, **62**, 77 (1942).

ditions and after-treatment give the highest yield and it is obscure why the yield of the hydroxymethyl compound rises by acetylation.

Since it became clear that the reaction of I with formaldehyde and hydrochloric acid gives a 5-substituted product, the same reaction was carried out on 5-ethyl-1-methyl-2(1*H*)-pyridone[8] (VII). A mixture of 3 g of VII, 1.04 g of paraformaldehyde, and 9 ml of conc. hydrochloric acid was reacted under the same conditions as in I and the reaction mixture was treated in the same manner from which 0.9 g (25%) of a pale yellow needles (VIII), mp 78—79°, $C_9H_{13}O_2N$, was obtained besides the recovery of 0.8 g of VII. The analytical values of VIII correspond to the introduction of one hydroxymethyl group into VII, and IR spectrum of VIII (in Nujol) showed absorptions for O–H at 3150 cm^{-1}, for amide C=O at 1665 cm^{-1}, for C–O at 1050 cm^{-1}, and lone H in the aromatic ring at 890 cm^{-1}.

The NMR spectrum (Fig. 2) of VIII (in $CDCl_3$) showed signals at 1.15 ppm (3H, triplet, J=8 cps, CH_2–$C\underline{H}_3$), 2.38 ppm (2H, quartet, J=8 cps, $\underline{CH}_2$–CH_3), 3.50 ppm (3H, singlet, N–CH_3), 4.55 ppm (3H, singlet, CH_2–OH), 7.05 ppm (1H, doublet, J=2 cps), and at 7.25 ppm (1H, doublet, J=2 cps). According to the NMR data of Jackman and Elvidge (loc. cit.), and of III, the protons at 3- and 5-positions should be present in a higher magnetic field than 7.05 ppm. Also, considering the fact that the peaks at 7.05 and 7.25 ppm have a coupling constant of 2 cps corresponding to the protons in *meta* position, VIII must be 5-ethyl-3-hydroxymethyl-1-methyl-2(1*H*)-pyridone. These data reveal that the 5-position in the pyridone ring is the most active, followed by the 3-position.

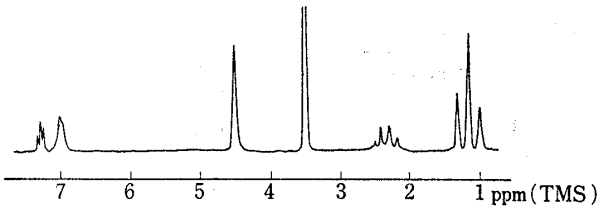

Fig. 2. NMR Spectrum of VIII in $CDCl_3$ (60 Mcps)

As one of the electrophilic substitution reactions on II with fused pyridone and benzene rings, the Friedel–Crafts reaction had been carried out.[5] The present reaction was also carried out with II in the same way as for I.

A mixture of 5 g of II, 2.04 g of paraformaldehyde, and 12.5 ml of conc. hydrochloric acid was stirred for 5.5 hr in an oil bath of 100°, 20 g of sodium acetate and 6 g of acetic anhydride were added, and the mixture was further stirred at 100° for 3 hr. Sodium acetate was filtered off from the cooled reaction mixture, the mixture was basified with potassium carbonate, and extracted with benzene. The benzene extract was dried and passed through a chromatographic column over alumina from which 0.9 g (15.2%) of pale yellow needles (IX), mp 158—160°, $C_{11}H_{11}O_2N$, was obtained, besides the recovery of 2.4 g of II. The analytical values of IX correspond to the introduction of one hydroxymethyl group into II. The IR spectrum of IX (in Nujol) exhibited absorptions for C–H at 3340 cm^{-1}, for amide C=O at 1635 cm^{-1}, for C–O at 1030 cm^{-1}, for lone 1-H of the aromatic ring at 897 cm^{-1}, and for adjacent

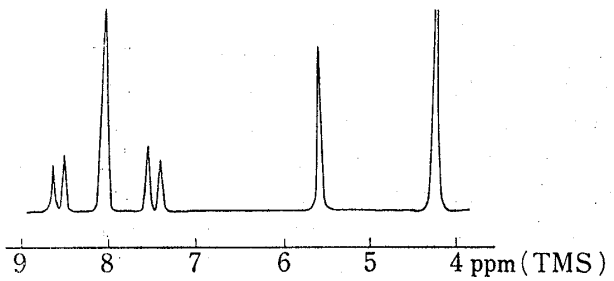

Fig. 3. NMR Spectrum of IX in CF_3CO_2H (60 Mcps)

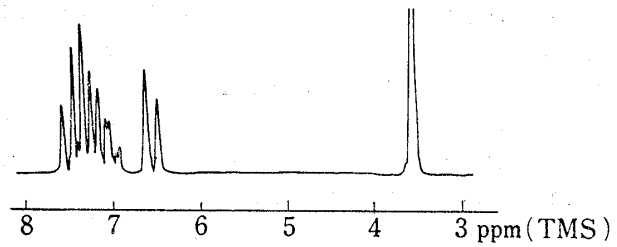

Fig. 4. NMR Spectrum of II in CF_3CO_2H (60 Mcps)

8) S. Sugasawa and M. Kirisawa, *Pharm. Bull.* (Japan), 3, 190 (1955).

two H of the aromatic ring at 825 cm^{-1}. The NMR spectrum (Fig. 3) of IX (in CF_3COOH) showed signal peaks at 4.25 ppm (3H, singlet, N–CH_3), 5.62 ppm (2H, singlet, $\underline{CH_2}OH$), 7.56 ppm (1H, doublet, J=9 cps), 8.12 ppm (3H, singlet), and 8.61 ppm (1H, doublet, J=9 cps). Comparison of these spectral data with the NMR spectrum (Fig. 4) of II (in CF_3COOH) showed that the protons at 3 (7.56 ppm) and 4 (8.61 ppm) in IX formed an AB-type quartet, as in II, so that it is clear that the hydroxymethyl group is not in the pyridone ring. From the fact that there is a lone H of the aromatic ring in the IR spectrum of IX, and from the comparison of the ultraviolet (UV) spectra of IX and 6-ethyl-1-methyl-2-(1*H*)-quinolone (X), it may be assumed that IX is 6-hydroxymethyl-1-methyl-2-(1*H*)quinolone but, in order to further confirm this structure, reaction outlined in Chart 2 were carried out.

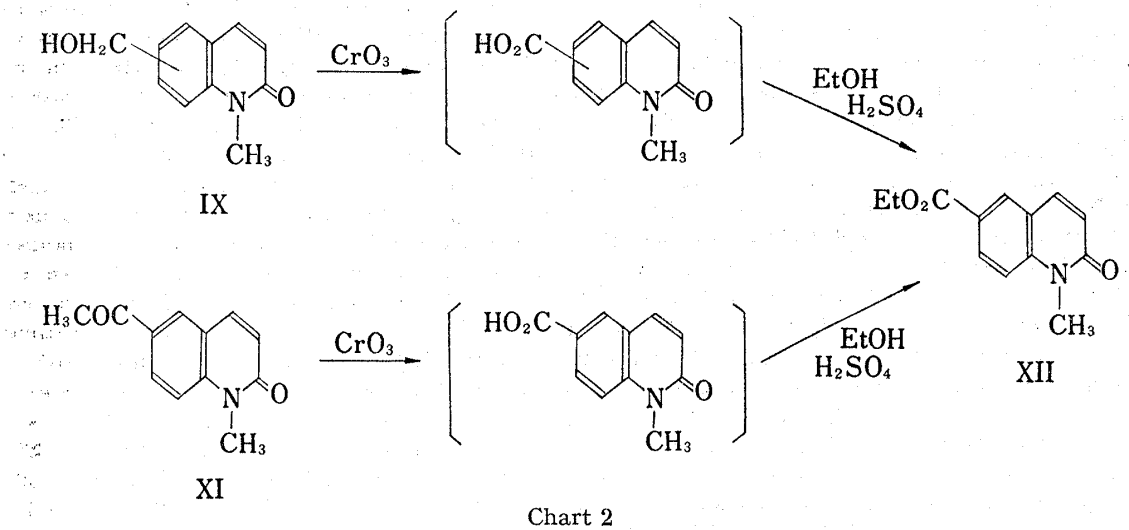

Chart 2

Oxidation of IX with chromium trioxide followed by esterification gave a product which was identified by the mixed melting point determination and IR spectral comparison with 6-ethoxycarbonyl-1-methyl-2(1*H*)-quinolone (XII), derived from 6-acetyl-1-methyl-2(1*H*)-quinolone (XI), whose structure had been chemically proved by Tomisawa and others.[5] Consequently, IX is 6-hydroxymethyl-1-methyl-2(1*H*)-quinolone, and the reaction of formaldehyde and hydrochloric acid on II is known to occur at 6-position.

Experimental[9]

5-Hydroxymethyl-1-methyl-2(1*H*)-pyridone (III)——A mixture of 10 g of I, 6 g of paraformaldehyde, and 30 ml of conc. HCl was stirred for 3 hr in an oil bath of 100°, 60 g of AcONa and 12 g of Ac_2O were added, and the mixture was further stirred at 100°. AcONa was filtered off and the filtrate was extracted with isoamyl alcohol. The extract was dried over $MgSO_4$, the solvent was evaporated under a reduced pressure, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was passed through a column of Al_2O_3, the effluent was evaporated, and the residue was recrystallized from acetone–benzene mixture to colorless needles, mp 106—108°. Yield, 5.9 g (46%). *Anal.* Calcd. for $C_7H_9O_2N$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.32; H, 6.72; N, 10.33. IR ν_{max}^{Nujol} cm^{-1}: 3280 (O–H), 1665 (amide C=O), 1025 (C–O), 910, 849 (δ C–H). NMR (in $CDCl_3$) ppm: 3.45 (3H, singlet, N–CH_3), 4.40 (3H, singlet, CH_2OH), 6.45 (1H, quartet, J=9, 1.5 cps, C_3–H), 7.38 (2H, C_4–H, C_6–H). UV λ_{max}^{EtOH} mμ (log ε): 233 (4.03), 310 (3.79).

5-Ethoxycarbonyl-1-methyl-2(1*H*)-pyridone (V)——A solution of 0.5 g of III dissolved in 30 ml of H_2O and added with 0.5 g of CrO_3 was allowed to stand over night. H_2O was evaporated and the residue was dissolved in 5 ml of conc. H_2SO_4. To this solution, 10 ml of abs. EtOH was added and the solution was warmed on a water bath for 3 hr. EtOH was evaporated from this mixture, the residue was neutralized with $NaHCO_3$, and extracted with benzene. The extract was dried over $MgSO_4$, and benzene was evaporated. Recrystallization of the residue from benzene afforded 0.183 g (29%) of pale yellow plates, mp 65—67°. *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.78; H, 6.15; N, 7.78. IR

9) All melting points are uncorrected.

ν_{max}^{KBr} cm^{-1}: 1725 (C=O), 1670 (amide C=O), 1290 (C–O), 840 (δ C–H). NMR (in $CDCl_3$) ppm: 1.41 (3H, triplet, $J=7$ cps, $CH_2\underline{CH_3}$), 3.75 (3H, singlet, N–CH_3), 4.43 (2H, quartet, $J=7$ cps, $\underline{CH_2}CH_3$), 6.66 (1H, doublet, $J=9$ cps, C_3–H), 8.02 (1H, quartet, $J=9$, $J=3$ cps, C_4–H), 8.48 (1H, doublet, $J=3$ cps, C_6–H).

5-Acetoxymethyl-1-methyl-2(1*H*)-pyridone (VI)——A mixture of 0.5 g of III and 3 g of Ac_2O was heated in an oil bath of 100° for 3 hr and excess Ac_2O was distilled off under a reduced pressure. Recrystallization of the residue from benzene–hexane gave 0.6 g (92%) of colorless needles, mp 45—47°. *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.71; H, 6.12; N, 7.74. IR ν_{max}^{Nujol} cm^{-1}: 1725 (C=O), 1660 (amide C=O), 1230 (C–O–C), 890, 820 (δ C–H). NMR (in $CDCl_3$) ppm: 2.02 (3H, singlet, $COCH_3$), 3.50 (3H, singlet, N–CH_3), 4.80 (2H, singlet, –$\underline{CH_2}OCOCH_3$), 6.55 (1H, doublet, $J=9$ cps, C_3–H), 7.35 (2H, multiplet, C_4–H, C_6–H).

5-Ethyl-3-hydroxymethyl-1-methyl-2(1*H*)-pyridone (VIII)——A mixture of 3 g of VII, 1.04 g of paraformaldehyde, and 9 ml of conc. HCl was stirred for 7 hr while heated in an oil bath of 100°, 5.1 g of AcONa and 2.5 g of Ac_2O were added, and the mixture was stirred for further 3 hr at 100°. AcONa was filtered off, the filtrate was extracted with isoamyl alcohol, and the extract was dried over $MgSO_4$. Isoamyl alcohol was evaporated under a reduced pressure and the residue as a benzene solution was passed through a chromatographic column over Al_2O_3. The column was eluted with benzene–$CHCl_3$ (1:1) and $CHCl_3$, the solvent was evaporated from these elutes, and the residue therefrom was recrystallized from benzene to pale yellow crystals, mp 78—79°. Yield, 0.9 g (25%). *Aanl.* Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.59; H, 7.91; N, 8.58. IR ν_{max}^{Nujol} cm^{-1}: 3150 (O–H), 1665 (amide C=O), 1050 (C–O), 890 (δ C–H). NMR (in $CDCl_3$) ppm: 1.15 (3H, triplet, $J=8$ cps, CH_2–$\underline{CH_3}$), 2.38 (2H, quartet, $J=8$ cps, $\underline{CH_2}$–CH_3), 3.50 (3H, singlet, N–CH_3), 4.55 (3H, singlet, CH_2OH), 7.05 (1H, doublet, $J=2$ cps), 7.25 (1H, doublet, $J=2$ cps).

6-Hydroxymethyl-1-methyl-2(1*H*)-quinolone (IX)——A mixture of 5 g of II, 2.04 g of paraformaldehyde, and 12.5 ml of conc. HCl was stirred for 5.5 hr while heating in an oil bath of 100°, 20 g of AcONa and 6 g of Ac_2O were added, and further stirred for 3 hr at 100°. AcONa was filtered off, the filtrate was basified with K_2CO_3, and extracted with benzene. The extract was dried over $MgSO_4$, benzene was evaporated, and the residue was submitted to column chromatography over Al_2O_3. The column was eluted with $CHCl_3$ and the residue left after evaporation of $CHCl_3$ was recrystallized from benzene–$CHCl_3$ mixture to pale yellow needles, mp 158—160°. Yield, 0.9 g (15.2%). *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.44; H, 6.08; N, 7.52. IR ν_{max}^{Nujol} cm^{-1}: 3340 (O–H), 1635 ((amide C=O), 1030 (C–O), 897, 825 (δ C–H). NMR (in CF_3COOH) ppm: 4.25 (3H, singlet, N–CH_3), 5.62 (2H, singlet, $\underline{CH_2}OH$), 7.56 (1H, doublet, $J=9$ cps, C_3–H), 8.12 (3H, singlet, C_5–H, C_7–H, C_8–H), 8.61 (1H, doublet, $J=9$ cps, C_4–H). UV λ_{max}^{EtOH} mμ (log ε): 235 (4.68), 250 (4.01), 275 (3.89), 284 (3.87), 341 (3.83).

6-Ethoxycarbonyl-1-methyl-2(1*H*)-quinolone (XII)——a) A solution of 0.15 g of IX dissolve din 10 ml of H_2O was stirred at room temperature while adding 0.21 g of CrO_3 and the mixture was stirred for 48 hr. H_2O was evaporated, 4 g of conc. H_2SO_4 and 5 ml of EtOH were added to the residue, and the mixture was refluxed for 6 hr. Excess EtOH was evaporated, the residue was poured into $KHCO_3$ solution, and the alkaline solution was extracted with benzene. The extract was dried over $MgSO_4$, benzene was evaporated, and the residue was recrystallized from benzene to pale yellow plates (XII), mp 145—146°. Yield, 0.07 g (38.2%).

b) A solution of 0.5 g of XI dissolved in 30 ml of H_2O was stirred at room temperature while adding 0.66 g of CrO_3 and the mixture was stirred for 48 hr. H_2O was evaporated, 9 g of conc. H_2SO_4 and 10 ml of EtOH were added to the residue, and the mixture was refluxed for 6 hr. Excess EtOH was evaporated, the residue was poured into $KHCO_3$ solution, and the alkaline solution was extracted with benzene. The extract was dried over $MgSO_4$, benzene was evaporated, and the residue was recrystallized from benzene to pale yellow plates, mp 145—146°. Yield, 0.07 g (12.2%). *Anal.* Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.81; H, 5.73; N, 6.19. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1650 (amide C=O), 830 (δ C–H).

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