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Studies on Tertiary Amine Oxides. LI.[1] Reactions of Quinoline and Isoquinoline N-Oxides with Propiolates and Methacrylonitrile

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The 1,3-dipolar cycloaddition between quinoline N-oxide (I) and methyl propiolate progressed in the presence of acetic anhydride or hydroquinone to afford methyl α-formyl-2-quinolineacetate (IIa). The reaction with ethyl propiolate in the presence of hydroquinone gave the corresponding ethyl ester (IIb). The reaction of I with methacrylonitrile in the presence of hydroquinone produced cyanohydrin of 2-acetonylquinoline (VIII) or 2-acetonylquinoline (IX) and 2-cyanoquinoline (X).

Isoquinoline N-oxide (XI) was less reactive and resisted the reaction with propiolates, but reacted with methacrylonitrile in the presence of hydroquinone to give 1-acetonylisoquinoline (XII), 1-cyanoisoquinoline (XIII) and isoquinoline.

A previous paper[3] of this series has described that the 1,3-dipolar cycloaddition between quinoline N-oxide and acrylic acid derivatives occurs in the presence of acetic anhydride or hydroquinone to give 2-substituted quinolines through primary cycloadducts, and acetic anhydride and hydroquinone are essential for the proceeding of reaction. As an extension of this study, reactions using propiolates and methacrylonitrile as 1,3-dipolarophile were investigated under similar conditions.

At first, reactions of quinoline N-oxide (I) with methyl and ethyl propiolates were carried out. A solution of I, methyl propiolate and 2 equivalents of acetic anhydride in dioxane was refluxed for 1 hour. Chromatography on alumina afforded methyl α-formyl-2-quinolineacetate (IIa) and carbostyril in 27.5 and 26% yields, respectively.

From the reaction in the presence of a catalytic amount of hydroquinone instead of acetic anhydride at 40° for 9 hours, IIa was obtained as a sole product in 33% yield.

The reaction of I with ethyl propiolate in the presence of hydroquinone at room temperature for 3 days also gave the corresponding ethyl ester (IIb) although in somewhat lower yield of 14.5%.

The infrared (IR) spectrum of IIa exhibited two carbonyl bands at 1683 and 1635 cm^{-1}, and the corresponding bands of IIb appeared at 1679 and 1635 cm^{-1}. The nuclear magnetic resonance (NMR) spectra of IIa and IIb showed the aldehyde proton as a singlet at τ 0.07 in each case. From mass spectra (M^+: IIa, *m/e* 229; IIb, *m/e* 243) and elemental analyses, their molecular formulas were decided to be $C_{11}H_{13}O_3N$ and $C_{12}H_{15}O_3N$, respectively.

However, IIa and IIb showed no signal peak characteristic of a methine proton in their NMR spectra, and displayed very weak absorption bands assignable to NH or OH stretching band in their IR spectra. Further the positive color test with ferric chloride indicates the presence of an enolizable carbonyl group in IIa and IIb. From these observations, the structure of II may be most likely formulated as the isomeric structure II-1 or II-2, the enamic

1) Part L: M. Hamana and S. Kumadaki, *Yakugaku Zasshi*, **95**, 87 (1975).
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3) M. Hamana, K. Funakoshi and Y. Kuchino, *Chem. Pharm. Bull.* (Tokyo), **22**, 1806 (1974).

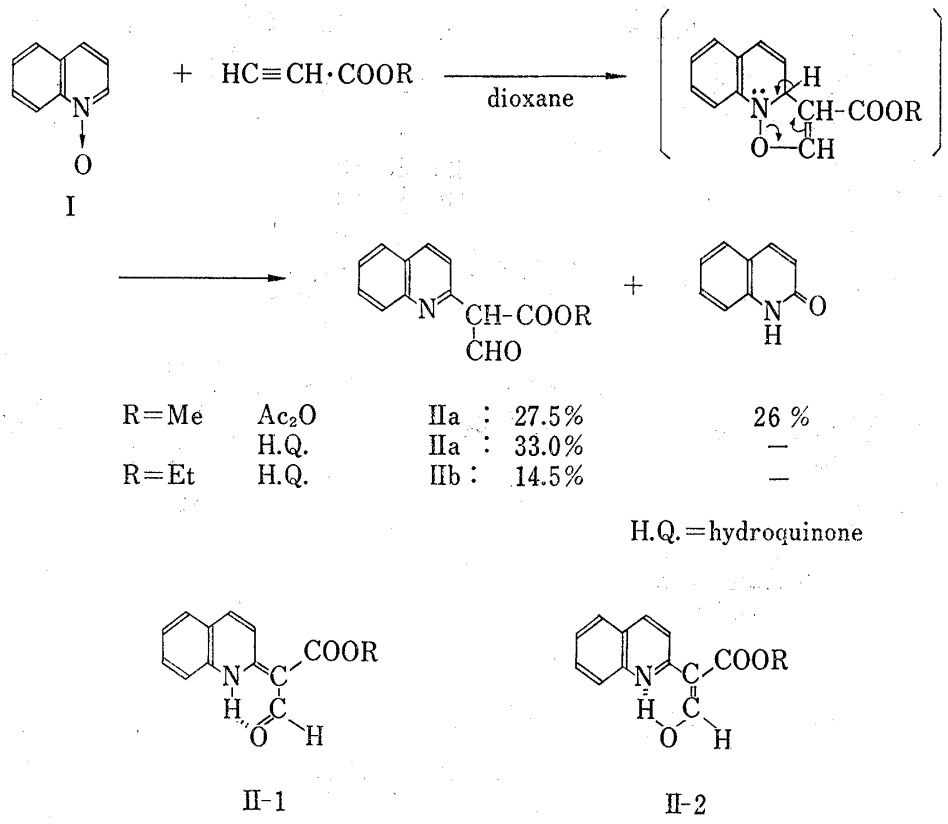


Chart 1

form II-1 being more favorable over the enolic one similarly to the cases of quinaldyl ketones reported previously[4] (Chart 1).

Apparently the reaction progressed through the primary cycloadduct as shown in Chart 1.

Some reactions of IIa and IIb were examined in connection with the confirmation of their structures. Oxidation of IIb with 30% hydrogen peroxide in acetic acid afforded quinaldic acid N-oxide, and hydrolysis of IIa with 6% sulfuric acid gave quinaldine (III). Treatment of IIa with excess lithium aluminium hydride in tetrahydrofurane at 50° yielded β-2-quinolylpropanol (IV) and quinoline; the courses of these reductions were not explored. In contrast to methyl α-formyl-1-methyl-2-benzimidazolacetate which was transformed into methyl 1-methyl-2-benzimidazolacetate on treatment with hydroxylamine,[5] IIa and IIb reacted normally with hydroxylamine to give the corresponding oximes (Va and Vb), and Vb was converted into ethyl 2-quinolinecyanoacetate (VI) by heating with phosphoryl chloride. The identity of VI was established by direct comparison with an authentic sample prepared from I and ethyl cyanoacetate by means of acetic anhydride.[6]

Further, ethyl 2-quinolinepyruvate (VII), the alternative product resulting from the cyclization of I and ethyl propiolate in opposite direction was prepared from quinaldine and diethyl oxalate.[7] In spite of detailed examination by means of its IR and NMR spectra, there was no visible sign of the presence of VII in the reaction mixture of I and ethyl propiolate.

These reactions are shown in Chart 2.

The reaction of I with methacrylonitrile in the presence of hydroquinone in dioxane gave rather curious results; one run afforded cyanohydrin of 2-acetonylquinoline (VIII) in 9%

4) M. Yamazaki, K. Noda and M. Hamana, *Chem. Pharm. Bull.* (Tokyo), **18**, 908 (1970).
5) S. Takahashi and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **12**, 1290 (1964).
6) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963).
7) W. Borsche and R. Manteuffel, *Ann.*, **562**, 22 (1936).

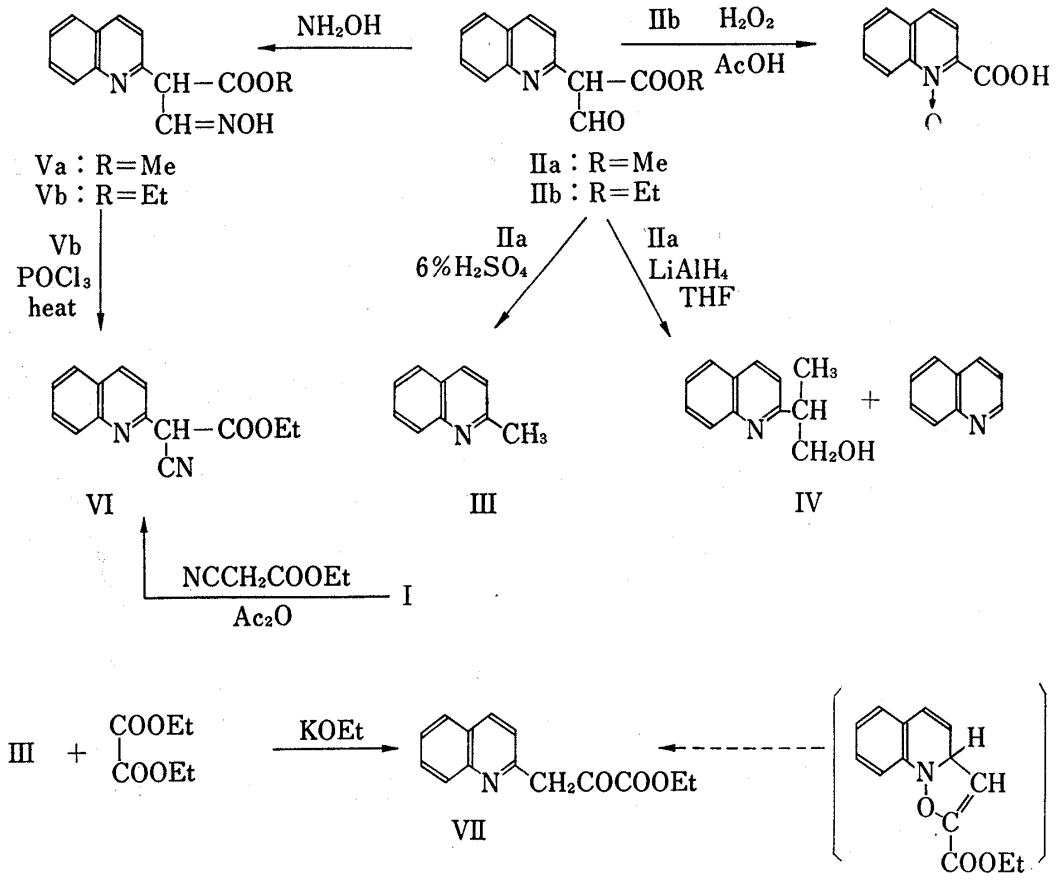


Chart 2

yield, and another run gave 2-acetonylquinoline (IX) and 2-cyanoquinoline (X) in 7 and 0.65% yields, respectively.

Compound IX was proved to be identical with an authentic sample obtained from I by the known routes.[8,9] The IR spectrum of VIII exhibited hydroxyl and nitrile bands at 3100 cm^{-1} and 2240 cm^{-1}, respectively, and the NMR spectrum showed the methylene protons as a singlet at τ 6.70 and the methyl protons as a singlet at τ 8.25.

Although it is not yet clear why different results were obtained from reactions under practically the same conditions, X should be considered to originate from unchanged I and hydrogen cyanide liberated during the reaction course. Because of the isolation of cyanohydrin VIII, it seems probable that VIII was initially formed and then converted into IX and hydrogen cyanide. In fact, IX was produced by heating VIII in dioxane in the presence of a small amount of hydroquinone. However, the direct breakdown of the primary cycloadduct into IX and hydrogen cyanide may be not excluded, and the details were not yet elucidated Chart 3).

The reaction of I with methacrylonitrile in the presence of acetic anhydride followed quite different path and resulted in the formation of a few kinds of polyquinolylmethanes. These and related results will be presented in another paper in the near future.

Isoquinoline N-oxide (XI) is appreciably less reactive toward reactions of above-mentioned type, and no definite product was obtained from the reaction with propiolates. However, the reaction with methacrylonitrile proceeded similarly in the presence of hydroquinone as shown in Chart 4. Differently from reactions of I, the cyanohydrin derivative was not isolated

8) T. Okamoto and H. Takayama, *Chem. Pharm. Bull.* (Tokyo), **11**, 514 (1962).
9) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **18**, 26 (1970).

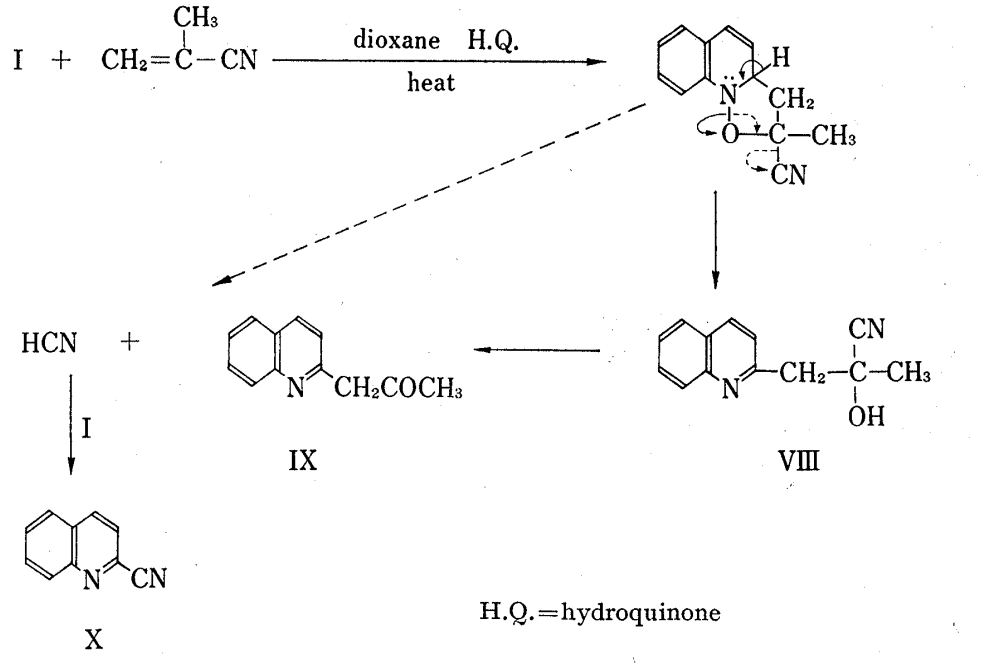
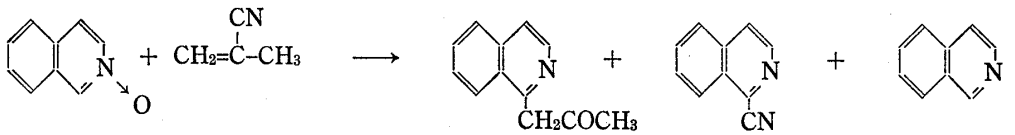


Chart 3



XI XII XIII

	XII	XIII	
DMF H.Q.	12%	5%	10%
dioxane H.Q.	3%	trace	10%

H.Q.=hydroquinone

Chart 4

and 1-acetonylisoquinoline (XII), 1-cyanoisoquinoline (XIII) and isoquinoline were obtained from reactions in dioxane and also dimethylformamide, the better yield being obtained from the reaction in dimethylformamide as compared with that in dioxane.

Experimental[10]

Reaction of Quinoline N-Oxide (I) with Methyl Propiolate——1) A solution of I (1.45 g), methyl propiolate (1.20 g) and Ac_2O (2.04 g) in dioxane (8 ml) was refluxed for 1 hr. The reaction mixture was evaporated *in vacuo*, made alkaline with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The ethereal solution of extracted substances was passed through an alumina column to give 0.63 g (27.5%) of methyl α-formyl-2-quinolineacetate (IIa) and then 0.3 g (25.5%) of carbostyril, mp 196—198°. IIa: yellow green needles, mp 170—171° (petr. benzine). IR ν_{max}^{Nujol} cm^{-1}: 1683, 1635 (C=O). NMR τ ($CDCl_3$): 0.07 (1H, s, -CHO), 1.2—2.5 (7H, m, aromatic protons and -CH-), 6.15 (3H, s, $-COOCH_3$). Mass Spectrum *m/e*: 229 (M^+), 214, 198, 170, 141, 128. *Anal.* Calcd. for $C_{13}H_{11}O_3N$: C, 68.11; H, 4.48; N, 6.11. Found: C, 67.88; H, 4.93; N, 6.00.

2) A solution of I (1.45 g), methyl propiolate (1.20 g) and hydroquinone (0.05 g) in dioxane (10 ml) was warmed at 40° for 9 hr and treated as described in 1) to give 0.75 g (33%) of IIa.

Reaction of I with Ethyl Propiolate——A solution of I (2.90 g), ethyl propiolate (2.65 g) and hydroquinone (0.10 g) in dioxane (10 ml) was kept at room temperature for 3 days. The reaction mixture was evaporated *in vacuo* and the residue was chromatographed on alumina with ether to give 0.70 g (14.5%) of ethyl α-formyl-2-quinolineacetate (IIb), yellow green needles, mp 120—121° (*n*-hexane). IR ν_{max}^{Nujol} cm^{-1}: 1679, 1635 (C=O).

10) All melting points are uncorrected. NMR spectra were measured with JNM-3H-60 spectrometers at 60 MC using trimethyl silane (TMS) as internal reference.

NMR τ ($CDCl_3$): 0.07 (1H, s, -C<u>H</u>O), 1.2—2.5 (7H, m, aromatic protons and -C<u>H</u>-), 5.69 (2H, q, J=7.5 Hz, -COOC<u>H</u>$_2$CH$_3$), 8.63 (3H, t, J=7.5 Hz, -COOCH$_2$C<u>H</u>$_3$). Mass Spectrum *m/e*: 243 (M^+), 214, 198, 170, 141, 128. *Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.39; H, 5.50; N, 5.71.

Oxidation of Ethyl α-Formyl-2-quinolineacetate (IIb) with H_2O_2-AcOH——A solution of IIb (0.10 g) and 30% H_2O_2 (5 ml) in AcOH (5 ml) was warmed at 70—80° for 6 hr. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized from EtOH-H_2O to give 0.01 g of quinaldic acid N-oxide, mp 160—161°. It was identified by comparison with an authentic sample.[11]

Hydrolysis of Methyl α-Formyl-2-quinolineacetate (IIa) with 6% H_2SO_4——A solution of IIa (0.20 g) in 6% H_2SO_4 (10 ml) was refluxed for 0.5 hr. The reaction mixture was made alkaline with 10% NaOH solution and extracted with $CHCl_3$. The petr. ether–ether (1: 1) solution of extracted substances was passed through an alumina column to give an oil, which was converted to a picrate, mp 192°. It was identical with an authentic sample of quinaldine picrate.

Reduction of IIa with $LiAlH_4$——To a solution of IIa (0.23 g) in tetrahydrofuran (THF) (40 ml) was added dropwise $LiAlH_4$ (0.23 g)–THF (40 ml), and the whole was warmed at 50° for 2 hr. The reaction mixture was treated with H_2O (20 ml) to decompose excess $LiAlH_4$ and shaken with CH_2Cl_2. The organic layer was separated and evaporated, and the residue was chromatographed on alumina. The fraction eluted with petr. ether–ether (1: 1) gave an oily mixture of two compounds, which was treated with picric acid to give 0.3 g of quinoline picrate. The ether eluate was kept at room temperature for several days to deposite crystals, which were recrystallized from petr. benzine to give 0.03 g of β-2-quinolylpropanol (IV), colorless prisms, mp 68—70°. IR ν_{max}^{Nujol} cm^{-1}: 3135, 1080 (OH). NMR τ ($CDCl_3$): 1.80—2.78 (6H, m, aromatic protons), 5.33 (1H, br. m, -C<u>H</u>-), 5.97 (2H, d, J=6.7 Hz, -C<u>H</u>$_2$OH), 6.81 (1H, br. m, -O<u>H</u>), 8.63 (3H, d, J=6.83 Hz, -CH-CH$_3$). *Anal.* Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.74; H, 6.87; N, 7.46.

Reactions of IIa and IIb with Hydroxylamine——1) A solution of IIb (0.10 g), AcONa (0.05 g) and $NH_2OH \cdot HCl$ (0.04 g) in EtOH (5 ml) was refluxed for 0.5 hr. Water was added. and precipitated crystals were filtered and recrystallized from EtOH to give 0.08 g of IIb-oxime (Vb), yellow needles, mp 189—191° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3150 (OH), 1650 (C=O), 1640, 1569 (C=N). *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.23; H, 5.49; N, 10.95.

2) Oxime of IIa (Va) was obtained in the similar way: yellow needles, mp 173—174° (decomp.) (EtOH).

Reaction of Vb with $POCl_3$——A mixture of Vb (0.10 g) and $POCl_3$ (3 ml) was refluxed for 3 hr and excess $POCl_3$ was removed *in vacuo*. The residue was treated with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was passed through an alumina column to give 0.02 g of ethyl 2-quinolinecyanoacetate (VI), yellow pillars, mp 166—167° (MeOH). It was proved identical with an authentic sample[6] prepared from I and ethyl cyanoacetate by means of Ac_2O.

Reaction of I with Methacrylonitrile——1) A solution of I (1.45 g), methacrylonitrile (0.67 g) and hydroquinone (0.05 g) in dioxane (10 ml) was heated at 90° for 12 days. The reaction mixture was evaporated *in vacuo*, made alkaline with $NaHCO_3$ solution and extracted with $CHCl_3$. The extracted substances were chromatographed on alumina with petr. ether–ether (1: 1) to give successively 0.01 g (0.65%) of 2-cyanoquinoline (X), colorless scales, mp 93—94° (*n*-hexane) and 0.12 g (7%) of 2-acetonylquinoline (IX), orange yellow pillars, mp 68—69° (petr. benzine). Picrate of IX: yellow needles, mp 175.5—176.5° (decomp.). The identity of IX was established by direct comparison with an authentic sample.[8,9]

2) Another run under practically the same condition followed by the same work up afforded 0.18 g (9.0%) of IX cyanohydrin (VIII), colorless needles, mp 121—123° (isopropyl ether). IR ν_{max}^{Nujol} cm^{-1} 3100 (OH), 2240 (CN). NMR τ ($CDCl_3$): 1.8—2.7 (6H, m, aromatic protons), 6.70 (2H, s, -C<u>H</u>$_2$-), 8.25 (3H, s, -C<u>H</u>$_3$). *Anal.* Calcd. for $C_{13}H_{12}ON_2$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.43; H, 5.69; N, 13.31.

Decomposition of VIII to IX——A solution of VIII (0.05 g) and hydroquinone (0.01 g) in dioxane (6 ml) was heated at 100° for 10 hr to give IX in an almost quantitative yield.

Reaction of Isoquinoline N-Oxide (XI) with Methacrylonitrile——1) A solution of XI (1.45 g), methacrylonitrile (0.67 g) and hydroquinone (0.05 g) in dimethyl formamide (DMF) (10 ml) was heated at 90° for 12 days, evaporated *in vacuo*, treated with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The benzene solution of extracted substances was passed through an alumina column. The first eluate gave 0.08 g (5%) of 1-cyanoisoquinoline (XIII), colorless needles, mp 88—89° (*n*-hexane). The second fraction afforded 0.12 g (10%) of isoquinoline, which was characterized as picrate, mp 220—222°. The last eluate gave 0.22 g (12%) of 1-acetonylisoquinoline (XII), yellow needles (*n*-hexane) (unstable crystals showing no definite mp). IR ν_{max}^{Nujol} cm^{-1}: 1597 (C=O). NMR τ ($CDCl_3$): 1.95—2.90 (6H, m, aromatic protons), 3.30 and 3.42 (1H, =C<u>H</u>-CO-

OH

and -C<u>H</u>=COH), 4.00 (1H, s, =C-O<u>H</u>), 7.82 (3H, s, =C-C<u>H</u>$_3$). Picrate: yellow scales, mp 191.5—192° (decomp.). *Anal.* Calcd. for $C_{12}H_{11}ON \cdot C_6H_3O_7N_3$: C, 52.18; H, 3.41; N, 13.52. Found: C, 51.92; H, 3.14; N, 13.53.

2) The same procedure using dioxane (10 ml) instead of DMF gave XII (3%), XIII (trace) and isoquinoline (10%).

11) Y. Hamada, *Yakugaku Zasshi*, **79**, 908 (1959).