

REDUCTIVE CYCLIZATION OF 3-(o-NITROBENZYLIDENE)-2,4-DIOXO-
PENTANOIC ACID AND ITS ESTER

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Catalytic reduction of 3-(o-nitrobenzylidene)-2,4-dioxopentanoic acid(1) and its methyl ester(2) in methanol gave 2-methyl-3-(α -hydroxy)quinoline-acetic acid 1-oxide(3), and methyl 1,4-dihydro-1-hydroxy-4-methoxy-2-methyl-3-quinolineglyoxylate (8) in 88% and 91% yields, respectively.

Cyclization of benzylidene compounds with ortho nitro group to heterocyclic compounds has widely been investigated¹.

Previously we reported the reductive cyclization of 3-(o-nitrobenzylidene)pentan-2,4-dione to give a mixture of 3-acetyl-quinaldine as minor product and the corresponding N-oxide as main one². On the continuation of this work, we now wish to report the convenient synthesis of 3-quinolineacetic acid 1-oxide and 1-hydroxy-1,4-dihydroquinoline by reductive cyclization of 3-(o-nitrobenzylidene)-2,4-dioxopentanoic acid(1), mp 183-185°, prepared by the Knoevenagel condensation of o-nitrobenzaldehyde with ethyl acetopyruvate in the presence of piperidine at 30°, and the corresponding methyl ester(2), mp 99-100°.

Catalytic hydrogenation of 1 over 5% Pd-C as catalyst in methanol (about three equivalent amounts of hydrogen were up-taken) gave a 88% yield of 2-methyl-3-(α -hydroxy)quinoline-acetic acid 1-oxide(3) as colorless needles, which was converted into the methyl ester(4) by action of diazomethane. The structure of 3, mp 243-244°(dec.), was deduced on the basis of the following evidence: ir ν max (KBr) 3450, 1700 cm^{-1} , uv λ EtOH $\text{nm}(\log \epsilon)$ 240(4.18), 320(3.85); nmr (DMSO- d_6) δ 2.67(3H, S, CH_3), 5.45 (2H, S, CH-OH), 8.55(1H, dd, $J=3,8$ HZ, $\text{C}_8\text{-H}$). Moreover manganese

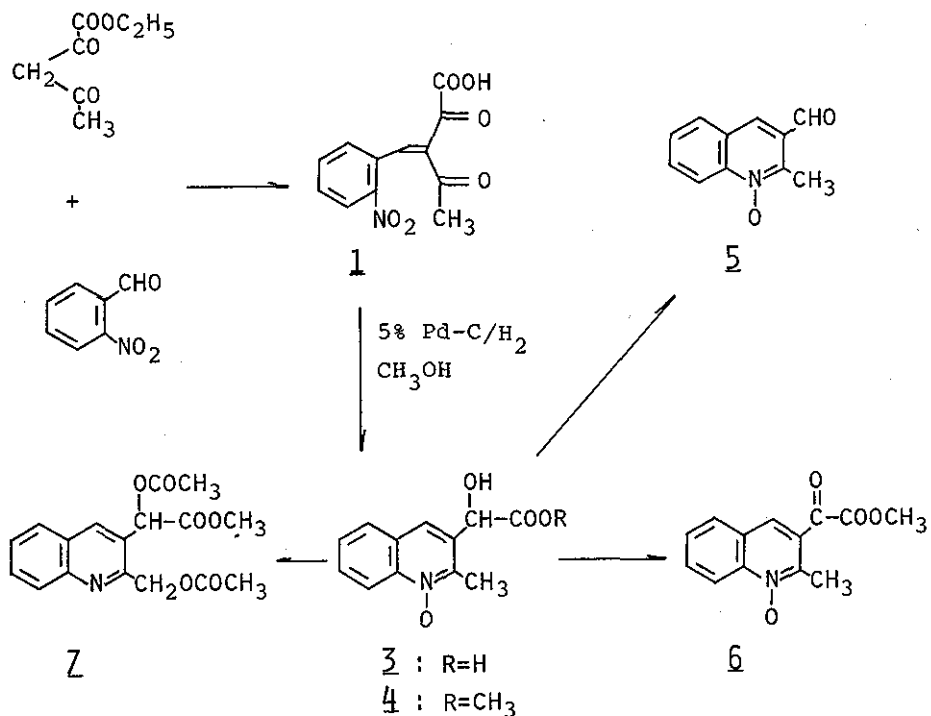


Chart 1

dioxide oxidation of 3 in dimethylsulfoxide and 4 in chloroform gave 2-methyl-3-quinolinecarboxyaldehyde 1-oxide(5)³ and methyl 2-methyl-3-quinolineglyoxylate 1-oxide(6) in good yields, respectively. Reaction of 4 with acetic anhydride gave a 75% yield of methyl 2-acetoxymethyl-3-(α -acetoxy)quinolineacetate(7), mp 84-85°, which is the general reaction of the aromatic amine N-oxide with alkyl substituents at 2-position⁴.

On the other hand, catalytic hydrogenation of 2 over 5% Pd-C in methanol (about two equivalent amounts of hydrogen were up-taken) gave methyl 1,4-dihydro-1-hydroxy-4-methoxy-2-methyl-3-quinolineglyoxylate(8) in 91% yield as colorless needles, mp 188-189°. The structure of 8 was confirmed on the basis of the following evidence: ir ν max (KBr) 1760, 1620, 1600 cm^{-1} ; uv $\lambda_{\text{max}}^{\text{EtOH}}$ nm(log ϵ) 246(4.03), 253(4.06), 264(3.58), 300(3.28), 332(3.74), 342(3.74); nmr (DMSO- d_6) δ 2.50(3H, s, CH_3), 3.38(3H, s, CO_2CH_3), 3.65(3H, s, OCH_3), 5.62(1H, s, CH), 11.65(1H, s, OH) This is soluble in aqueous sodium hydroxide solution and is hydrolyzed to the corresponding carboxylic acid(10) when heated at 75°. Treatment of 8 with acetic anhydride at 70° gave 1-acetoxy derivative(11), mp 188-189°, whose ir spectrum showed the strong absorption band at 1815 cm^{-1} due to $>\text{NOCOCH}_3$ ⁵. Reduction of 8 with zinc dust in acetic acid gave methyl 1,4-dihydro-4-methoxy-2-methyl-3-quinolineglyoxylate(12) in good yield, which was alternatively obtained by catalytic reduction of 11 over 5% Pd-C as catalyst. These chemical reactions are well known in 1-hydroxy-1,4-dihydroquinolin-4-one derivatives⁵ and will strongly support

the presence of $>N-OH$ group in compound 8.

Likewise the same reduction of 2 in ethanol gave the corresponding 4-ethoxy derivative(9), mp 163-164°.

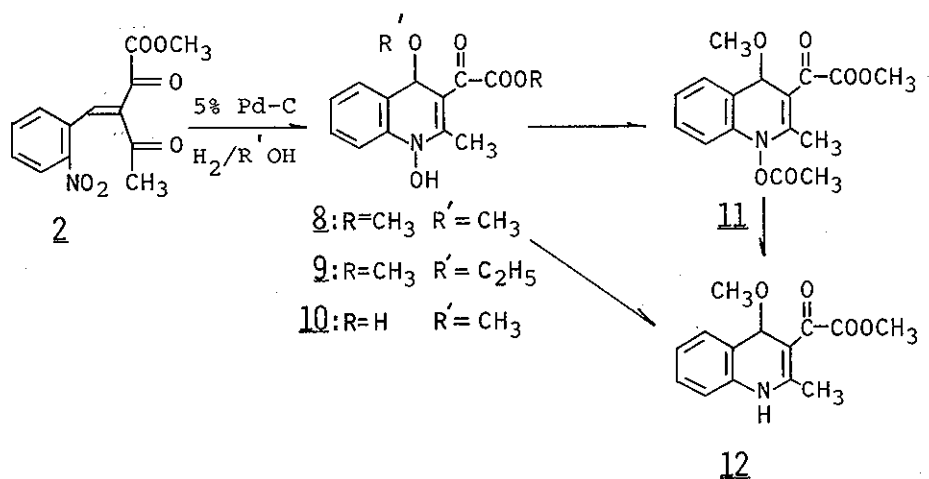


Chart 2

The mechanism of the formation of quinoline N-oxide(3) and 1,4-dihydroquinolines(8, 9) were postulated as drawn in Chart-3.

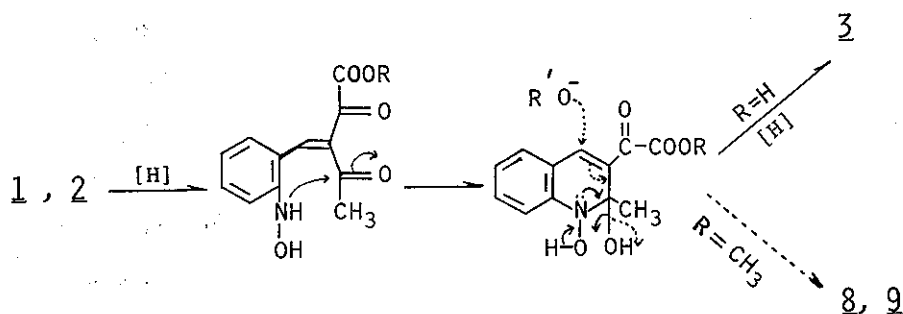


Chart 3

REFERENCES

- 1 P.N. Preston and G. Tennant, Chem. Rev., 72, 627(1972), and references cited therein.
- 2 T. Kurihara, H. Sano, and H. Hirano, Chem. Pharm. Bull., 23, 1155(1975).
- 3 4: colorless needles, ir ν max (KBr) 1745 cm^{-1} ; ur λ $\overset{\text{EtOH}}{\text{max}}$ nm(log ϵ) 239(4.15), 322(3.87); nmr (DMSO- d_6) δ 2.65(3H, S, CH_3), 3.70(3H, S, COOCH_3), 5.60(1H, d, J=6 Hz, CHOH), 6.65(1H, d, J=6 Hz, D_2O exchangeable, CHOH), 8.60(1H, dd, J=3, 8 Hz, $\text{C}_8\text{-H}$). 5: pale yellow needles, ir ν max (KBr) 1710 cm^{-1} ; nmr (CDCl_3) δ 3.00(3H, S, CH_3), 8.75(1H, dd, J=3, 8 Hz, $\text{C}_8\text{-H}$), 10.35(1H, S, CHO). 6: yellow needles, ir ν max (KBr) $1730, 1700\text{ cm}^{-1}$; nmr (CDCl_3) δ 2.90(3H, S, CH_3), 4.05(3H, S, COOCH_3), 8.70(1H, dd, J=3, 8 Hz, $\text{C}_8\text{-H}$). 7: colorless needles, ir ν max (KBr) 1730 cm^{-1} ; nmr (CDCl_3) δ 2.12, 2.25(each 3H, each S, $2\times\text{OCOCH}_3$), 3.77(3H, S, COOCH_3), 5.75(2H, S, CH_2), 6.55(1H, S, CH), 8.75(1H, dd, J=3, 8 Hz, $\text{C}_8\text{-H}$). 11: colorless needles, ir ν max (KBr) $1815, 1760, 1600\text{ cm}^{-1}$; uv λ $\overset{\text{EtOH}}{\text{max}}$ nm(log ϵ) 213(4.43), 240(4.30), 280(3.47, sh), 292(3.59), 325(3.96). 12: colorless needles, mp $231\text{-}232^\circ$, ir ν max (KBr) 1760 cm^{-1} ; nmr (DMSO- d_6) δ 2.42(3H, S, CH_3), 3.30(3H, S, COOCH_3), 3.60(3H, S, OCH_3), 5.45(1H, S, CH), 8.10(1H, dd, J=3, 8 Hz, $\text{C}_8\text{-H}$).
- 4 S. Ginsburg and I.B. Wilson, J. Am. Chem. Soc., 79, 481(1957).
- 5 J.D. Loudon and I. Welling, J. Chem. Soc., 1960, 3470.

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