THE REACTION OF 4-METHOXYQUINOLINE 1-OXIDE WITH DIMETHYL ACETYLENEDICARBOXYLATE

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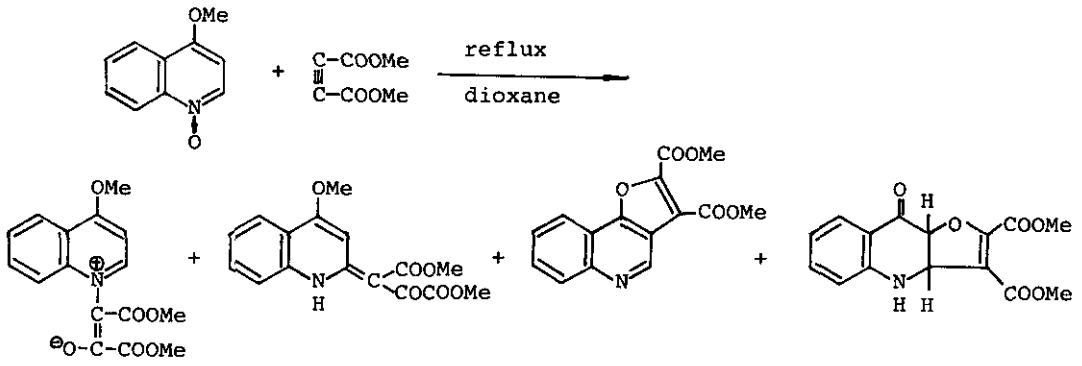
Abstract — 4-Methoxyquinoline 1-oxide reacts with dimethyl acetylenedicarboxylate in boiling dioxane affords N-quinolinium ethylide (1), 2-substituted quinoline (2), furo[3,2-c]quinoline (3) and 9-oxo-tetrahydro-cis-furo[3,2-b]quinoline (4). Similar reactions readily proceed at low temperatures in dichloromethane, acetonitrile and DMF to give 2, 3 and 4.

We have recently studied the 1,3-dipolar cycloaddition of some 3-monosubstituted and 3,4-disubstituted quinoline 1-oxides, and have obtained many interesting results[1]. This paper mainly deals with our observations on the reaction of 4-methoxyquinoline 1-oxide with dimethyl acetylenedicarboxylate, which was carried out in connection with the above studies.

Treatment of 4-methoxyquinoline 1-oxide with dimethyl acetylenedicarboxylate (1 equiv.) in boiling dioxane for 1 hr gave α-[N-(4-methoxyquinolinium]-α,β-bismethoxycarbonyl-β-oxo-ethylide (1) (8.8%), methyl α-methoxycarbonyl-α-[2-(4-methoxyquinolyl)]pyruvate (2) (31.5%), 2,3-bismethoxycarbonylfuro[3,2-c]quinoline (3) (12.2%) and 3a,4,9,9a-tetrahydro-2,3-bismethoxycarbonyl-9-oxo-cis-furo[3,2-b]-quinoline (trace). While the reaction at room temperatures in dioxane was very slow, similar reactions readily proceeded even at lower temperatures when dichloromethane, acetonitril or DMF was used as a solvent instead of dioxane, and products 2, 3 and 4 were obtained, but no formation of N-ylide 1 was noticed in these cases. Table I summarizes thses results.

Table I. The Reaction of 4-Methoxyquinoline 1-Oxide with Dimethyl Acetylenedicarboxylate



1 2 3 4

Solvent	Reaction temp.(°C)	Reaction time(hr)	Product, Yield(%) 1	2	3	4
dioxane	101	1	8.8	31.5	12.2	trace
CH_2Cl_2	-10	1	-	1.7	9.8	4.6
CH_2Cl_2	0	1	-	22.1	9.2	8.1
MeCN	0	0.5	-	18.8	-	4.6
DMF	0	1	-	34.0	19.5	5.9

Structure assignments of the products are based on the satisfactory elemental analyses, and the IR and PMR spectra shown in Table II. Further, the structure of the 2,3-dihydroquinoline 4 was unambiguously established by an X-ray diffraction study[2].

Canonne et al.[3] have recently reported that the reaction of 4-chloroquinoline 1-oxide (5) with diethyl acetylenedicarboxylate in boiling toluene gave the 2-substituted product (6) (mp 91-92°; 3.1%) and the furo[3,2-c]quinoline (7) (3.7%). While the PMR spectra of furoquinolines, 3 and 7, were closely similar to each other, the spectral pattern of 2 was found to be considerably different from that of 6 reported as the 2-substituted product by them.

In order to explore the structure of 2, 2 was oxidized by heating with 30% hydrogen peroxide and acetic acid to give 4-methoxyquinaldic acid 1-oxide (8), from which methyl 4-methyoxyquinaldate (9) was obtained upon successive treatment with

Table II. The Some Physical Properties of the Products

Products	IR (cm^{-1})	PMR ($CDCl_3$) δ (ppm)
1 Yellow needles mp 209-211°	νC=O : 1680, 1725	3.60 (3H, s, $COOCH_3$), 3.94 (3H, s, $COOCH_3$), 4.28 (3H, s, 4-OCH_3), 7.16 (1H, d, $J_{2,3}$=7 Hz, C_3-H), 7.68-8.44 (4H, m, Ar-H), 8.64 (1H, d, $J_{2,3}$=7 Hz, C_2-H)
2 Colorless scales mp 163-165°	νC=O : 1690, 1725	3.76 (3H, s, $COOCH_3$), 3.88 (3H, s, $COOCH_3$), 4.12 (3H, s, 4-OCH_3), 7.32-7.80 (3H, m, Ar-H), 8.05 (1H, dd, $J_{7,8}$=8 Hz, $J_{6,8}$=2 Hz, C_8-H), 8.10 (1H, s, C_3-H), 15.40-16.00 (1H, br s, NH)
3 Colorless needles mp 148-149°	νC=O : 1725	4.06 (3H, s, $COOCH_3$), 4.07 (3H, s, $COOCH_3$), 7.58-8.44 (4H, m, Ar-H), 9.40 (1H, s, C_2-H)
4 Yellow prisms mp 142-145°	νNH : 3320 νC=O : 1645, 1710, 1740	3.80 (3H, s, $COOCH_3$), 3.87 (3H, s, $COOCH_3$), 5.17 (1H, d, $J_{2,3}$=10 Hz, C_2-H), 5.35 (1H, d, $J_{2,3}$=10 Hz, C_3-H), 6.68 (2H, m, Ar-H), 7.36 (1H, m, Ar-H), 7.78 (1H, dd, $J_{5,6}$= 8 Hz, $J_{5,7}$=2 Hz, C_5-H)
6' Yellow needles mp 135-136°	νC=O : 1690, 1725	1.36 (6H, m, two CH_3), 4.30 (4H, m, two CH_2), 7.44-7.88 (3H, m, Ar-H), 8.09 (1H, dd, $J_{7,8}$=8 Hz, $J_{6,8}$=2 Hz, C_8-H), 16.20-17.00 (1H, br s, NH)

phosphorus trichloride and methanol[4]. Compound 9, colorless needles, mp 146-147°, was proved identical with an authentic sample prepared in the same way from ethyl 4-methoxy-2-quinolinecyanoacetate[5]. Thus, product 2 was established as the 2-substituted quinoline.

This result prompted us to re-examine the reaction described by Canonne et al.[3] Treatment of 5 with diethyl acetylenedicarboxylate (1 equiv.) for 1 hr in boiling toluene gave not the reported 6 but instead another product (6')(4.6%) together with 7 (9.6%). Product 6', yellow needles, mp 135-136°, has the empirical formula $C_{17}H_{16}ClNO_5$, and the IR and PMR spectra are consistent with the 2-substituted quinoline structure. Heating 6' with 30% hydrogen peroxide and acetic acid afforded 4-chloroquinaldic acid 1-oxide (10), yellow needles, mp 164-165°. Compound 10 was identical with a sample prepared by a similar oxidation of ethyl 4-chloro-2-quinolinecyanoacetate easily obtainable from 5 and ethyl cyanoacetate by means of acetic anhydride. Accordingly, the structure proposed by Canonne et al.[3] for 6

should be assigned to product 6′ isolated by us. Comparison of the PMR spectra of 2 and 6′ (Table II) further supports this conclusion; it seems likely that product 6 obtained by Canonne et al. is a different type of compound.

These reactions are formulated in Chart 1.

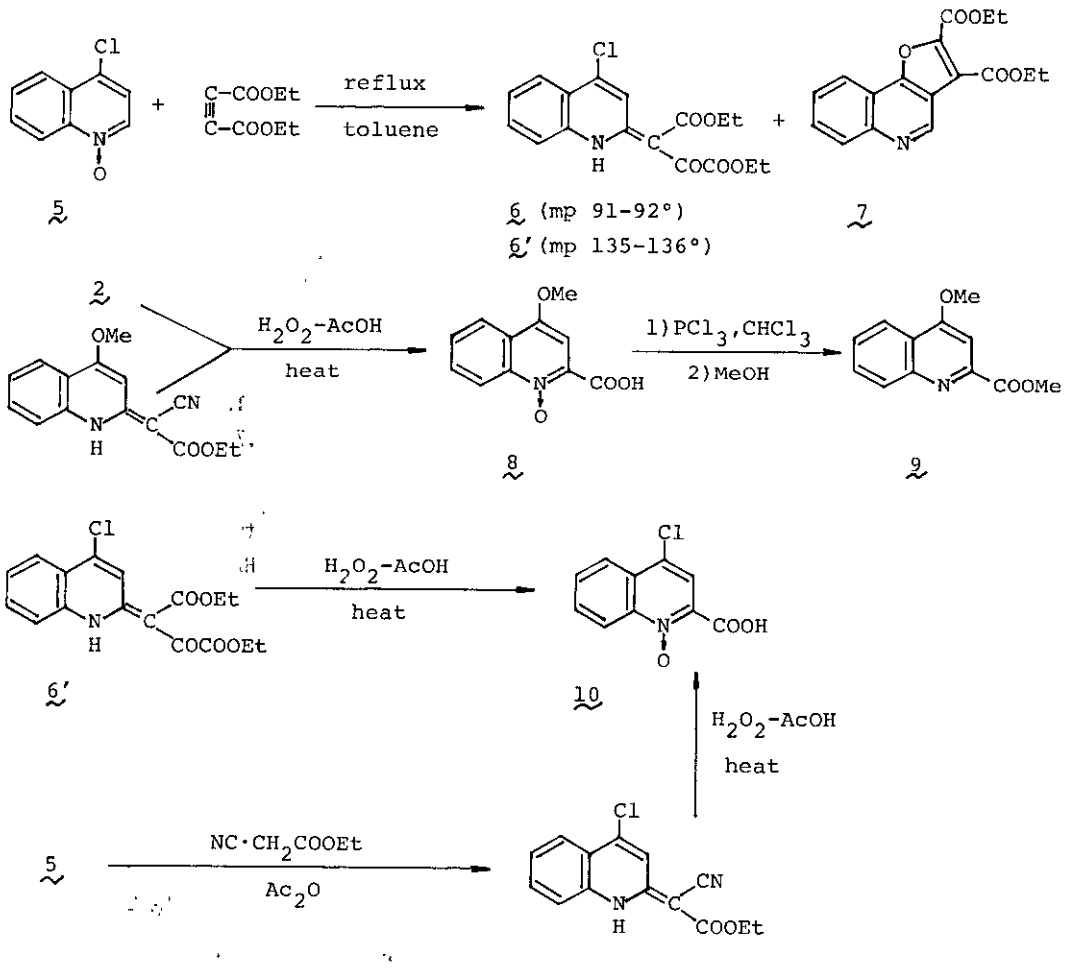


Chart 1

The primary 1,3-cycloadduct (A) initially formed from 4-methoxyquinoline 1-oxide and dimethyl acetylenedicarboxylate is not stable enough to be isolated, and readily undergoes the N-O bond fission. The formation of the N-ylide 1, the 2-substituted quinoline 2 and the furo[3,2-c]quinoline 3 can be explained by courses a, b and c, respectively, as formulated in Chart 2[6]. However it is difficult at present to rationalize the formation of 9-oxo-tetrahydro-furo[3,2-b]quinoline 4. Course a involves the rearrangement of A to the aziridine intermediate (B), which

isomerizes to 1. The concerted loss of the α-proton with the N-O bond fission in A gives 2 (course b). The formation of 3 follows course c which involves the successive formation of the 2,3-dihydroquinoline (C) and the 3,4-dihydroquinoline (D), and elimination of methanol from D.

Although the de-methylation of the 4-methoxy group of the quinoline ring is inevitable, the formation of 4 is very much noticeable because 4 is the first example of 2,3-dihydroquinolines obtained from the 1,3-dipolar cycloaddition of quinoline 1-oxides. The reaction seems likely to proceed through the 2,3-dihydroquinoline intermediate (E) different from D, however the details of the mechanism is not clear at all, particularly with respect to the de-methylation process. Furthermore, the intermediacy of E postulated above suggests the possibility that the formation of the 2-substituted quinoline 2 follows an alternate path involving E as a precursor, instead of course b[6,7].

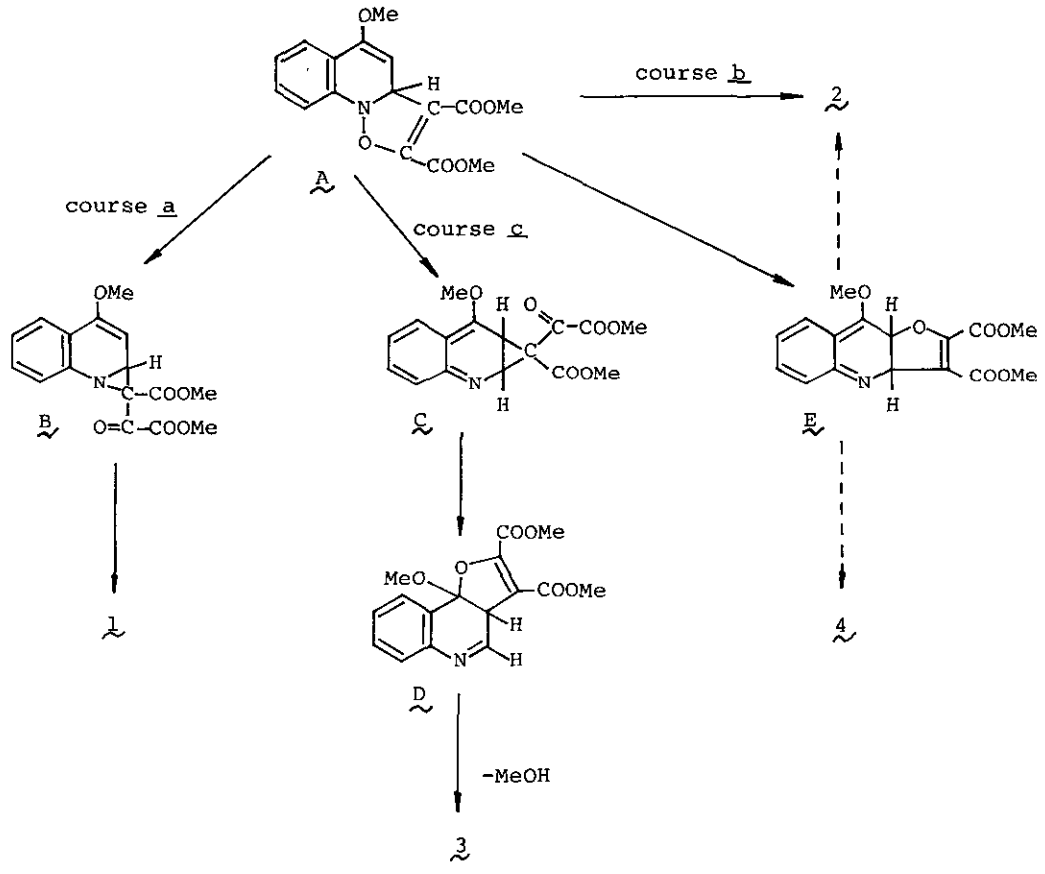


Chart 2

Further studies are in progress in order to clarify the essential features of the formation of 4 by using various 4-substituted quinoline 1-oxides and dipolarophiles.

ACKNOWLEDGEMENT

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