A NOVEL FORMATION OF CYCLOPROPA[c]QUINOLINES FROM SOME 2-SUBSTITUTED QUINOLINE N-OXIDES

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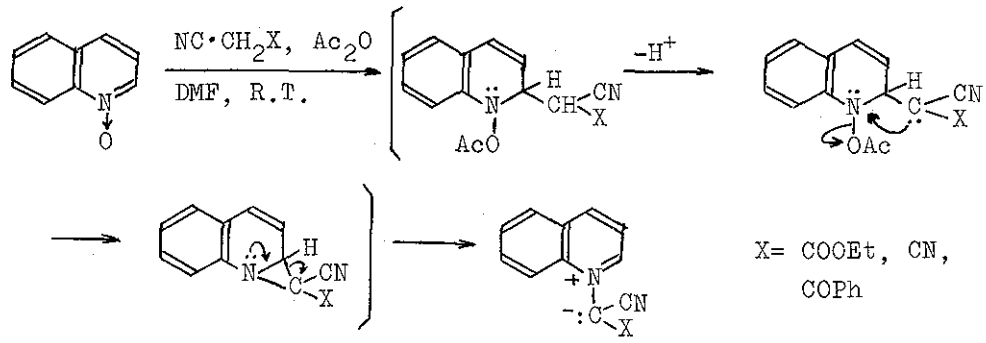
2-Chloroquinoline N-oxide (1) reacts with ethyl cyanoacetate in the presence of benzoyl chloride and triethylamine to give ethyl 1-cyano-2-oxo-1a,2,3,7b-tetrahydrocyclopropa[c]quinoline-1-carboxylate (2) in 78% yield. The reaction of 2-phenylquinoline N-oxide also affords ethyl 1-cyano-2-phenyl-1a,7b-dihydrocyclopropa[c]quinoline-1-carboxylate though in a lower yield. The reaction of 1 with malonodinitrile gives not a cyclopropaquinoline but 1-benzoyloxy-2-(α,α-dicyanomethylene)-1,2-dihydroquinoline.

It is now well known that nucleophilic reaction of aromatic N-oxide in the presence of an acylating agent is highly varied depending upon the natures of N-oxide and reagents as well as the reaction conditions[1,2]. The N-ylide formation shown below is one of the new reactions encountered in our laboratory[3,4].



We now wish to report a novel reaction of another type which was observed when some 2-substituted quinoline N-oxides were treated with ethyl cyanoacetate in the presence of benzoyl chloride and triethylamine, leading to cyclopropa[c]quinolines.

To an ice-cooled solution of 2-chloroquinoline N-oxide (1) and ethyl cyanoacetate (2 equiv.) and triethylamine (2 equiv.) in chloroform was added benzoyl chloride (1.5 equiv.), and the reactants were allowed to react overnight at room temperatures. Purification by chromatography through silica gel gave ethyl 1-cyano-2-oxo-1a,2,3,7b-tetrahydrocyclopropa[c]quinoline-1-carboxylate (2) in a good yield of 78%.

Product 2 forms colorless needles of mp 224-226°, and its structure assignment is based on the satisfactory elemental analysis [$C_{14}H_{12}O_3N_2$], the IR spectrum [ν_{max}^{Nujol} cm^{-1}: 2280 (C≡N) and 1728, 1675 (C=O)], the mass spectrum [m/e: 256 (M^+), 211 (M^+-OC_2H_5) and 210 (M^+-C_2H_5OH)], and the PMR and CMR spectra shown in Table I and II. The stereochemistry of 2 was deduced as formulated in Chart 1 from comparison of the ethyl signals in the PMR spectrum with those of diethyl 1,2-dicyano-1a,1b,2,7b-tetrahydro-

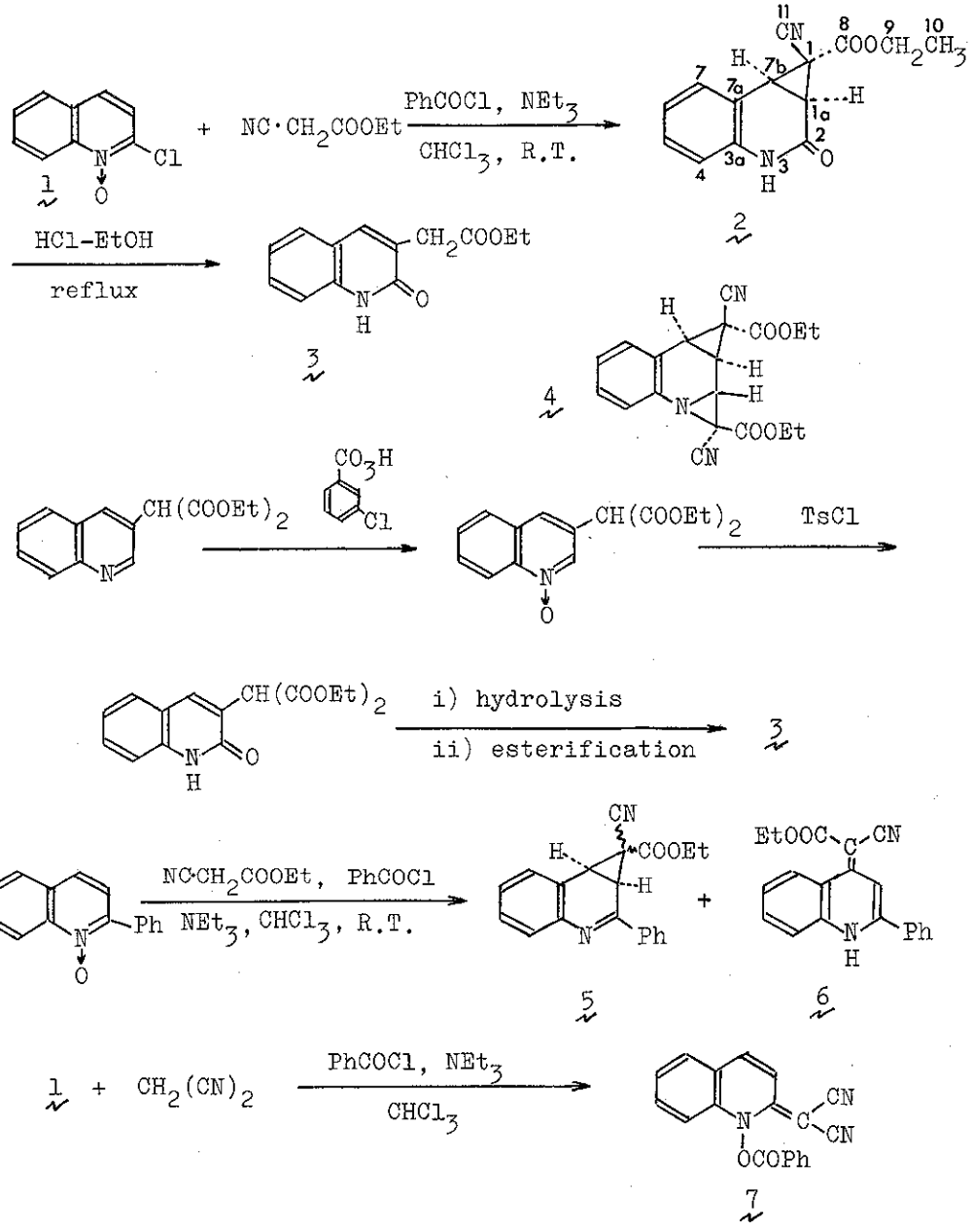


Chart 1

1H-azirino[1,2-a]cyclopropa[c]quinoline-1,2-dicarboxylate (4), the stereochemistry of which had been unambiguously established by the X-ray analysis[5,6].

Refluxing 2 with ethanol saturated with hydrogen chloride for 2 hr yielded 3-ethoxycarbonylmethylcarbostyril (3), colorless pillars, mp 181-182°, which was proved identical with an authentic sample prepared from diethyl 3-quinolylmalonate[6] through its N-oxide as shown in Chart 1.

Table I. PMR Chemical Shifts of 2 (δ) (DMSO-d_6)

$COOCH_2\underline{CH_3}$ [a]	C_{1a}-H	C_{7b}-H	$COO\underline{CH_2}CH_3$ [b]	aromtic-H	CO-N<u>H</u>-
1.3(t) J=6.0 Hz	3.13(d) J=8.1 Hz	3.78(d) J=8.1 Hz	4.32(q) J=6.0 Hz	6.96-7.66(m)	10.88(s)

a) The methyl protons of 4 appear at δ 1.28 (6H, t, J=7.6 Hz).
b) The methylene protons of 4 appear at δ 4.24 (2H, q, J=7.6 Hz) and 4.28 (2H, q, J=7.6 Hz).

Table II. CMR Chemical Shifts of 2 (δ) (DMSO-d_6)

Number of carbon (off-resonance)				
	1	1a	2	3a
	20.37(s)	35.70(d)	160.92(s)	136.73(s)
	4,5,6,7	7a	7b	8
	130.11(d) 129.34(d) 122.70(d) 115.43(d)	114.07(s)	33.82(d)	165.44(d)
	9	10	11	
	63.29(t)	13.74(q)	113.12(s)	

The reaction of 2-phenylquinoline N-oxide with ethyl cyanoacetate under the same conditions also gave a cyclopropa[c]quinoline, ethyl 1-cyano-2-phenyl-1a,7b-dihydrocyclopropa[c]quinoline-1-carboxylate (5), colorless pillars, mp 181°, though in a lower yield of 17.6%, accompanied with a small amount of ethyl 2-phenyl-4-quinolinecyanoacetate (6), yellow pillars, mp 232°, (8%).

No cyclopropaquinoline was obtained from attempted reactions of quinaldine N-oxide and 2-cyanoquinoline N-oxide. The reaction of 1 with malonodinitrile also gave not a cyclopropaquinoline but instead 1-benzoyloxy-2-(α,α-dicyanomethylene)-1,2-dihydroquinoline (7), yellow needles, mp 152-153°, in a small yield of 13%.

Identification of 5, 6 and 7 was performed by elemental analyses and the IR, PMR, CMR and mass spectrometry. We are now plannig an X-ray diffraction study in order to elucidate the stereochemistry of 5.

The formation of 2 may be rationalized by the course formulated in Chart 2. The 1,4-dihydroquinoline intermediate (8) formed from the benzoyl chloride-adduct of 1 looses a proton. Subsequently, the extrusion of benzoyloxy anion from this anionic intermediate (9), with the concerted attack of the anion center on the electron-deficient 3-position of the quinoline ring, leads to a cyclopropaquinoline (10), which is hydrolyzed to 2 possibly during work-up. It must be pointed here that the transformation of 9 into 10 is apparently the same pattern with the formation of aziridine intermediate in the first-mentioned N-ylide formation.

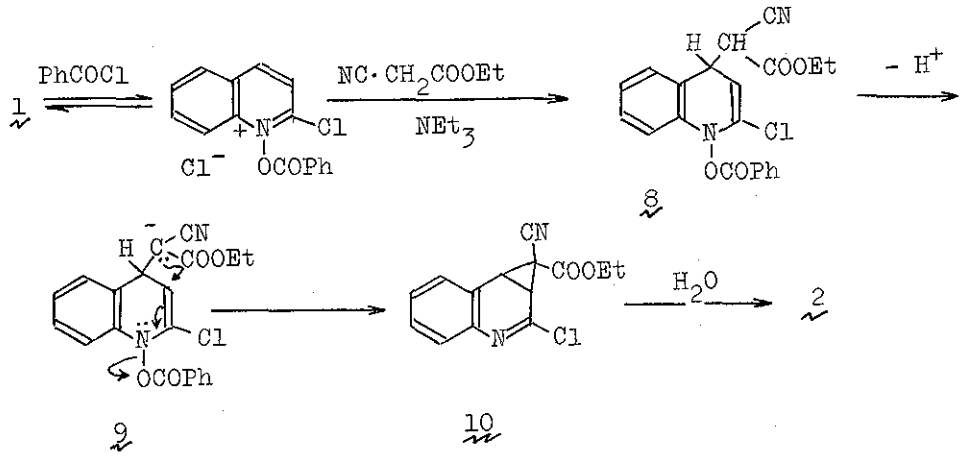


Chart 2

Further studies are in progress to widen the scope of this type of reaction.

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