QUINOLINE DERIVATIVES

I. SYNTHESIS OF QUINOLINE DERIVATIVES VIA 1,2,3,4-TETRAHYDROQUINOLINE

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A number of substituted tetrahydroquinolines were dehydrogenated for the first time to the corresponding quinoline derivatives by means of chloranil and a cupric chloride–pyridine complex. It is shown that the tendency for dehydrogenation decreases on passing from 6-formyl- to 6-bromo-, 6-nitro-, and 7-nitrotetrahydroquinolines. The nitration of N-acyltetrahydroquinolines (where the acyl group is formyl, acetyl, or benzoyl) was studied in detail. The possible formation of a 7-nitro isomer in addition to a 6-nitro isomer was demonstrated, and conditions which make it possible to vary the ratio of the yields of these isomers were found.

The considerable difficulties associated with the preparation of various substituted quinolines and consisting in the extremely low yields of products (5-10%) and the obtaining, as a rule, of a difficult-to-separate mixture of isomers compelled us to search for new routes for the synthesis of these compounds. The latter compounds open up wide possibilities for the preparation of a number of new compounds – intermediate in the synthesis of physiologically active substances.

A method of synthesis of various substituted indole via dehydrogenation of the corresponding indoline derivatives has become well known in recent years [1]. In this communication we present some data from a study of the possibility of the application of this method to the quinoline series. With this end in view, the starting quinoline was converted to 1,2,3,4-tetrahydroquinoline (THQ) by catalytic hydrogenation in an autoclave on an $Ni-Cr_2O_3$ industrial catalyst [2]; acylation of the THQ gave its N-acyl derivatives (where the acyl group is acetyl or benzoyl), and reduction of the quinoline with formic acid [3] gave N-formyl-THQ. Since quinoline and THQ behave differently in electrophilic substitution reactions (the substituents enter the 5 and 8 positions in quinoline and 6 and 7 positions in THQ), finding effective media for the dehydrogenation of these derivatives would make it possible to synthesize the inaccessible 6- and 7- substituted quinolines.

The literature contains an extremely small amount of information on the dehydrogenation of substituted THQ: 6,8-dinitro-THQ is dehydrogenated with chromic anhydride in sulfuric and acetic acid [4], while 6-acetyl-THQ is dehydrogenated with mercuric acetate [5]. In order to study the possibility of dehydrogenation of various THQ derivatives we selected the following compounds: 2-methyl-, 6-bromo-, 6-formyl-, and 6- and 7-nitrotetrahydroquinoline. 6-Bromo-THQ was obtained by bromination of THQ in chloroform [6], and 6-formyl-THQ was obtained by the rearrangement of N-formyl-THQ in the presence of phosphorus oxychloride [7]. 7-Nitro-THQ was obtained by the action of a nitrating mixture on THQ [8] with a certain change in the treatment of the reaction mass which made it possible to raise the yield from 66 to 88%. The N-alkyl analogs of THQ behave similarly, while the N-acetyl-THQ behaves differently, since nitration of it gives the 6- and 7-nitro isomers in 37 and 20% yields, respectively [9].

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TABLE 1. Results of the Nitration of N-Acyl-THQ

Starting compound	Density (d) of nitrating agent (HNO_3)	amount of nitrating agent, moles	H_2SO_4 conc., %	Yield, %	
				6-isomer	7-isomer
N-Formyl-THQ*	1,35	1	98	48	6
	1,35	2	91	41	—
	1,35	2	98	53	13
	1,35	1	93	46	5
	1,45	1	98	53	—
	1,45	2	98	64	3
N-Acetyl-THQ	1,35	2	98	30	30
	1,45	1	98	55	—
	1,45	2	98	64	6
N-Benzoyl-THQ	1,45	1	98	50	—
	1,45	2	98	68	5

*Only 6-Nitro-THQ was obtained in 10% yield by nitration with benzoyl nitrate in absolute acetonitrile [15].

TABLE 2. Results of the Dehydrogenation of Tetrahydroquinoline Derivatives

Compound	Cupric chloride-pyridine			Chloranil		
	Time, h	yield of quinoline derivative, %	recovery of THQ derivative, %	Time, h	yield of quinoline derivative, %	recovery of THQ derivative, %
2-Methyl-THQ	3,0	41,5	23,6	5	15	Pronounced resinification
	3,5	51,0	25,4	4	51,8	11
6-Formyl-THQ	6,5	11,4	6,4	8,5	45,4	5
	10	25,0	52,6	12,0	48,3	5
6-Bromo-THQ	10	38,73	25,4	7	—	67,3
	12	39,5	15,3	15	66,6—71,1	Not detected
7-Nitro-THQ	5	—	74,0	7	—	67
	10	14,25	71,3	15	44,6—58,0	Not detected
6-Nitro-THQ	10	—	73,0	7	—	71,2
	15	8,0	72,5	14	20—26	20—30

In order to elucidate the reason for the formation of the 7-nitro isomer, the nitration of N-acyl-THQ (where the acyl group is formyl, acetyl, or benzoyl) was investigated in detail as a function of the nitrating agent [concentrated nitric acid (sp. gr. 1.45 or 1.35) or benzoyl nitrate], medium (concentrated sulfuric acid, acetic anhydride, or acetonitrile), temperature, and reaction time (Table 1).

It was shown that the form of the acyl shield on the nitrogen atom of the THQ molecule has little effect on the product yields. The maximum yield of the 6-nitro isomer (64-68%) is achieved with a nitrating mixture consisting of concentrated sulfuric acid and a twofold excess of nitric acid (sp. gr. 1.45); in the process, the yield of the 7-nitro isomer decreases to 3-6%.

When a nitrating mixture containing less concentrated nitric acid (sp. gr. 1.35) is used, the yield of the 7-nitro isomer increases to 13-30%, while the yield of the 6-nitro isomer decreases to 30-53%. In each case, the 6-nitro derivatives are isolated as the N-acyl derivatives, while the 7-nitro isomer is isolated as an infusible sulfate which is slightly soluble in organic solvents.

These investigations provide a basis for assuming that the yield of 7-nitro-THQ depends directly on the proton concentration in the reaction medium. This sort of thinking is in agreement with the results obtained in a study of the kinetics and mechanism of the acid hydrolysis of N-acyl-THQ. A study of the effect of sulfuric acid concentrations from 0.96 to 69.79% at 25-94 deg on the course of the hydrolysis indicated that the rate-determining step in the hydrolysis is bimolecular and that water and a proton enter as catalysts into the composition of the activated complex. In other words, not only N-acyl-THQ but also activated complex [N-acyl-THQ + H_3O^+] exists and is nitrated in a solution of N-acyl-THQ in sulfuric and nitric acids, i.e., it can be assumed that the formation of the 7-nitro isomer depends on the existence of a hydronium ion in the reaction medium.

We also accomplished the dehydrogenation of the substituted THQ by means of a cupric chloride-pyridine complex and chloranil. It was established that the rate of dehydrogenation (Table 2) depends substantially on the presence of substituents in both the benzene and piperidine rings.

Thus, while 2-methyl-THQ is dehydrogenated quite readily (50% yield after 3.5-4 h), the introduction of electron-accepting substituents into the benzene ring of THQ markedly inhibits dehydrogenation. Moreover, the tendency for dehydrogenation decreases with increasing electron-accepting properties of these substituents on passing from 2-methyl- to 6-formyl-, 6-bromo-, 7-nitro-, and 6-nitro-THQ. Thus, using a cupric chloride-pyridine complex, 6-formyl-THQ and 7-nitro-THQ are converted to 29% and 14.25%, respectively, of the corresponding quinoline derivatives after 10 h, while 6-nitro-THQ is generally not dehydrogenated under these conditions. The above order of substituents also holds for the dehydrogenation with chloranil. A comparison of these two dehydrogenating agents favors chloranil, since the yields of the corresponding quinolines are somewhat higher when it is used.

EXPERIMENTAL

1,2,3,4-Tetrahydroquinoline (THQ) [2], N-formyl-THQ [3], 6-bromo-THQ [6], and 6-formyl-THQ [7] were obtained via well-known methods. The constants and yields of these compounds were in agreement with the literature data.

7-Nitrotetrahydroquinoline. A nitrating mixture consisting of 8.1 g (0.1 mole) of concentrated HNO_3 (sp. gr. 1.45) and 40 ml of concentrated H_2SO_4 was added with cooling to a solution of 13.3 g (0.1 mole) of THQ in 100 ml of concentrated H_2SO_4. The reaction mixture was held at −10 to 0 deg for 3 h and then poured over ice. The dark-red solution was made alkaline with ammonium hydroxide while cooling with an ice-salt mixture. The resulting pale-rose precipitate of 7-nitro-THQ contaminated with ammonium sulfate was filtered through a filter with a porous bottom, and the 7-nitro-THQ was washed with ethanol. The ethanol was removed to give 11 g (62%) of orange-red crystals with mp 63.5-64 deg (from ethanol) (mp 63-64 deg [8]). An additional amount (4.7 g) of 7-nitro-THQ was isolated by ether extraction from the alkaline mother liquor. The overall yield was 15.7 g (88%). UV spectrum (in ethanol), λ_{max}, nm (log ε): 262 (4.19), 405 (3.2).

Nitration of N-Acyltetrahydroquinolines with a Nitrating Mixture – Synthesis of 6-Nitrotetrahydroquinolines. A solution of 1 mole of N-acyl-THQ in concentrated sulfuric acid was added dropwise to a nitrating mixture consisting of 2 mole of nitric acid (sp. gr. 1.45) and a threefold excess of concentrated sulfuric acid. The resulting yellow solution was poured over ice, and the pale-yellow precipitate, which is a mixture of 6-nitro-N-acyl-THQ and7-nitro-THQ sulfate, was filtered. This mixture was refluxed with alcohol, and the insoluble 7-nitro-THQ sulfate was separated in the form of pale-yellow cyrstals with mp 220 deg (dec.); 6-nitro-N-acyl-THQ was isolated from the mother liquor by evaporation of the alcohol.

6-Nitro-N-formyl-THQ. This was obtained in the form of gold plates with mp 137-137.5 deg (from ethanol). UV spectrum, λ_{max}, nm (log ε): 224 (4.12), 324 (5.13) (ethanol). Found %: C 57.47, 57.32; H 4.94, 4.92. $C_{10}H_{10}N_2O_3$. Calc. %: C 58.25; H 4.89.

6-Nitro-N-acetyl-THQ. This was obtained as yellow crystals with mp 115-117 deg. Found %: C 59.48, 59.54; H 5.21, 5.15. $C_{11}H_{12}N_2O_3$. Calc. %: C 60.00; H 5.48.

6-Nitro-N-benzoyl-THQ. This was obtained as white needles with mp 134-135 deg (mp 135 deg [9]). UV spectrum (ethanol), λ_{max}, nm (log ε): 326 (4.52).

The precipitate of 7-nitro-THQ sulfate was dissolved in hot water and made alkaline with ammonium hydroxide. The resulting 7-nitro-THQ was isolated by extraction with ether.

6-Nitro-THQ was isolated by refluxing 6-nitro-N-acyl-THQ with concentrated hydrochloric acid for 0.5-1 h. The solution wasmade alkaline with ammonium hydroxide and extracted with ether. Removal of the ether yielded brown crystals with mp 162-163 deg. UV spectrum (ethanol), λ_{max}, nm (log ε); 269 (3.61), 319 (3.69), 401 (4.21). According to [9], the melting point is 161-162 deg.

Dehydrogenation of substituted 1,2,3,4-Tetrahydroquinolines. A. A pyridine solution of 0.0135 mole of the compound to be dehydrogenated was added to a solution of 8.1 g (0.06 mole) of cupric chloride in 45 ml of pyridine, and the mixture was refluxed for 10-12 h. After cooling, the reaction mixture was poured into water, and the mixture was neutralized with ammonium hydroxide and extracted with ether. The solvent was removed by distillation from the dried ether solution, and the residue was distilled to collect the appropriate quinoline derivatives.

B. A mixture of 0.01 mole of the compound to be dehydrogenated and 4.92 g (0.02 mole) of chloranil in 75 ml of absolute p-xylene was refluxed for 10-15 h. After cooling, the xylene layer was separated from

the precipitate, and the precipitate was washed several times with 5% aqueous NaOH, water, and HCl (1:1). The acid extracts were treated at 0 deg with a saturated aqueous sodium nitrate solution, the resulting white precipitate of the N-nitroso derivative of THQ was filtered, and the aqueous mother liquor was neutralized with 20% aqueous NaOH. The dehydrogenation product was isolated by the usual method.

The dehydrogenation and identification of the compounds obtained were monitored chromatographically [on a loose layer of aluminum oxide in alcohol–heptane (1:3), development with iodine vapors] from the refractive indexes and the melting points of the picrates. Polarographic analysis (with a sodium tetraborate solution background) was used to determine the degree of dehydrogenation.

The quinaldine obtained had bp 80 deg (1 mm) and n_D^{22} 1.616 and gave a picrate with mp 191 deg (from a benzene) [bp 135.5 (26 mm), n_D^{24} 1.6126, picrate mp 191 deg [10]]. The quinoline-6-aldehyde obtained had mp 74-75 deg (from heptane) [mp 75-76 deg [11]]. The 6-bromoquinoline obtained had bp 96-98 deg (1 mm), mp 20-21 deg, and gave a picrate with mp 215-215.5 deg [bp 284 deg, mp 24 deg, picrate mp 215-216 deg (from benzene) [12]]. The 6-nitroquinoline obtained had mp 148-149 deg [mp 150 deg (from ethanol) [13]]. The 7-nitropuinoline obtained had mp 132 deg [mp 133 deg (from ethanol) [14]].

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