INVESTIGATION OF QUINOLINE DERIVATIVES

III.* DINITRO DERIVATIVES OF 1,2,3,4-TETRAHYDROQUINOLINE

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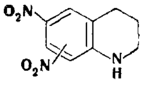
Some dinitro derivatives of 1,2,3,4-tetrahydroquinoline and its N-acyl analogs were synthesized. The structures of the dinitro isomers obtained were confirmed by NMR, UV, and IR spectroscopic data.

Several dinitro isomers of the 1,2,3,4-tetrahydroquinoline (THQ) series were synthesized to obtain potential physiologically active THQ derivatives. In the present study, the previously obtained [2] 6-nitro- (I) and 7-nitro-THQ (II) and their N-acyl analogs were nitrated in order to synthesize the dinitro isomers.

Except for 6,8-dinitro-THQ (III) [3-5], dinitro derivatives of the tetrahydroquinoline series are unknown in the literature. The methods described in the literature for the synthesis of this compound reduce to nitration of various N-substituted THQ in a aprotic solvent with fuming nitric acid. We obtained this same isomer in 50% yield by nitration of N-formyl-THQ with a nitrating mixture containing a twofold amount of nitric acid (sp. gr. 1.45).

The nitration of I with a nitrating mixture consisting of HNO_3 (sp. gr. 1.35) and 93% sulfuric acid gives only one dinitro isomer. Considering the orientation rules (the presence of a nitro group and a quaternary nitrogen atom and methylene group of the piperidine ring), one can expect the production of three reaction products:



III–V

III $8\text{-}NO_2$
IV $7\text{-}NO_2$
V $5\text{-}NO_2$

The compound that we obtained is not the 6,8-isomer: it differs form an authentic sample of the 6,8-dinitro derivative [3] with respect to R_f value, melting point, and UV and NMR spectra. The negative Janovsky reaction [6, 7], which consists in the appearance of intense coloration on treatment of a compound containing meta-oriented nitro groups with acetone and alkali, attests to the ortho orientation of the nitro groups in the molecule. The choice in favor of the 6,7-dinitro isomer (IV) was made on the basis of an analysis of the NMR spectra of IV and its N-formyl derivative, which are characterized by a small splitting of the broadened singlet in the region of absorption of benzene protons with the following chemical shifts: −8.00 ppm (in trifluoroacetic acid) for N-formyl-6-7-dinitro-THQ (VI); −7.57 ppm (in trifluoroacetic acid) and 7.89 ppm (in dimethyl sulfoxide) for 6,7-dinitro-THQ (IV).

The nitration of II with a nitrating mixture containing nitric acid (sp. gr. 1.45) gives 5,7-dinitro-THQ (VII), which can be isolated in 5-10% yield only when the reaction is carried out at 0° and the reaction mass is worked up directly after mixing of the reagents. The process is accompanied by pronounced resinification. This sort of resinification was also noted in the indoline series [8] (indoline is a THQ analog).

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*See [1] for communication II.

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TABLE 1. Results of Nitration of 7-Nitro-N-acyl-THQ

Acyl	Ratio of dinitro isomers of THQ	
	5,7-	7,8-
Formyl	5	1
Acetyl	2	1
Chloroacetyl	Base	Traces in the mother liquor
Trifluoroacetyl	11	1
Benzoyl	Base	None

TABLE 2. 7-Nitro-N-acyl-THQ

Compound	Acyl	Appearance	mp, °C*	Empirical formula	Found, %		Calc., %	
					C	H	C	H
VIII	Formyl	Brown needles	90	$C_{10}H_{10}N_2O_3$	58.2	5.0	58.3	4.9
IX	Acetyl	Brown crystals	104 102-103 [9]					
X	Trifluoroacetyl	Light-yellow plates	99-100	$C_{11}H_9F_3N_2O_3$	48.5	3.5	48.2	3.3
XI	Chloroacetyl	Colorless powder	108	$C_{11}H_{11}ClN_2O_3$	51.8	4.4	51.8	4.3
XII	Benzoyl	Light-rose crystals	154 153-154 [9]					

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*All of the compounds were purified by recrystallization from ethanol.

The nitration of N-formyl- (VIII), N-acetyl- (IX), N-chloroacetyl- (X), N-trifluoroacetyl-(XI), and N-benzoyl-7-nitro-THQ (XII) was studied. Compounds VIII and IX were obtained by refluxing II with HCOOH and acetic anhydride, while X, XI, and XII were obtained by refluxing with the appropriate acid chlorides. The yields were 85-90%.

The nitration of VIII-XII was carried out with a nitrating mixture consisting of HNO_3 (sp. gr. 1.35) and concentrated H_2SO_4 at -10 to 0°. In this case, nitration of 7-nitro-N-benzoyl-THQ with subsequent removal of the benzoyl protecting group gives only one compound, which is identical to the 5,7-dinitro-THQ (VII) obtained above with respect to R_f value and UV and NMR spectra. In all the remaining cases (Table 1), the formation of a second dinitro derivative was also observed. Starting from the orientation rules, one might have expected the formation of 6,7- (IV) or 7,8-dinitro-THQ (XIII). The derivative obtained proved to be the 7,8-dinitro isomer, since it differed from the previously synthesized 6,7-dinitro-THQ. When the conditions for nitration of 7-nitro-N-acetyl-THQ (IX) were changed, we still were unable to obtain the 6,7-dinitro isomer. The absence of 7,8-dinitro-THQ (XIII) in the case of the nitration of 7-nitro-N-benzoyl-THQ (XII) is probably associated with steric hindrance, since the benzoyl group is sterically bulky and hinders the entry of a second nitro group into the 8 position. However, a comparison of the yields of these isomers in the nitration of IX and XI, which contain acetyl and trifluoroacetyl groups, which are close in volume but differ with respect to electronic effects, indicates that it is necessary to take into account not only steric but also electronic effects.

Chromatographic monitoring of the trend of these reactions demonstrated that basically 100% conversion of the N-acyl derivatives of 7-nitro-THQ occurs after 6 h and is not accompanied by deacylation. We were unable to separate the 5,7- and 7,8-dinitro isomers as their acyl derivatives because of their close solubilities and R_f values. A mixture of these dinitro derivatives was subjected to acid hydrolysis and was then separated preparatively in a thin layer on plates.

All of the dinitro derivatives of THQ obtained and their acyl analogs are brightly colored needles that have sharp melting points, are quite soluble in alcohol, acetone, and ether, and insoluble in petroleum ether.

The positions of the nitro groups in all of the synthesized dinitro isomers were confirmed by means of the NMR spectra recorded in dimethyl sulfoxide (DMSO) solution. Two singlets with chemical shifts of 7.60 and 8.26 ppm are observed in the spectrum of 6,8-dinitro isomer (III). The spectrum of isomeric 5,7-dinitro-THQ (VII) contains two singlets with chemical shifts of 6.73 and 7.70 ppm, while the spectrum of the 7,8-derivative (XIII) is characterized by two doublets with chemical shifts of 6.91 and 7.20 ppm; this indicates the existence of two ortho-oriented 5-H and 6-H protons.

The electronic absorption spectra make it possible to distinguish dinitro compounds with meta and ortho orientations of the nitro groups. Thus the UV spectrum of the meta isomers (5,7- and 6,8-) is intense and is shifted to the shorter-wave region than the corresponding spectra of the ortho isomers (6,7- and 7,8-). In addition, in contrast to the o-dinitro isomers, the meta isomers give a positive Janovsky reaction [6, 7].

EXPERIMENTAL

6-Nitro-THQ (I) and 7-Nitro-THQ (II). These compounds were obtained by previously described methods [2].

6,8-Dinitro-THQ (III). A 16.1 g (0.1 mole) sample of N-formyl-THQ was added dropwise with water cooling to a mixture of 12.6 g (0.2 mole) of HNO_3 (sp. gr. 1.45) and 30 ml of concentrated H_2SO_4. The dark-red solution was held at room temperature for 12 h and poured into 100 g of ice. The precipitate was removed by filtration and washed with water, and the resulting bright-yellow needles with mp 162° (from ethanol) were refluxed for 1 h with 80 ml of concentrated hydrochloric acid. The hot solution was filtered, and the mother liquor was cooled to give 10.4 g (48%) of greenish needles with mp 165° (from ethanol) (mp 165-166° [5]). UV spectrum (in ethanol), λ_{max}, nm (log ε); 215 (4.12), 270 (4.00), 360 (4.20).

6,8-Dinitro-N-acetyl-THQ (XIV). A 2.2-g (0.01 mole) sample of 6,8-dinitro-THQ was refluxed for 1 h with 10 ml of acetic anhydride, and the resulting solution was poured into 100 ml of ice water. The precipitate was removed by filtration and washed with water. The yellow crystals had mp 155°. Found: C 49.7; H 3.9%. $C_{11}H_{11}N_3O_5$. Calculated: C 50.0; H 4.1%.

6,8-Dinitro-N-benzoyl-THQ (XV). This compound was similarly obtained from 6,8-dinitro-THQ and excess benzoyl chloride. The yellow crystals had mp 163°. Found: C 58.6; H 3.9%. $C_{16}H_{13}N_3O_5$. Calculated: C 58.7; H 4.0%.

6,7-Dinitro-THQ (IV). A solution of 4.4 g (0.25 mole) of 6-nitro-THQ in 100 ml of concentrated H_2SO_4 was added dropwise with ice-cooling to a mixture of 2.5 ml of nitric acid (sp. gr. 1.35), 80 ml of concentrated H_2SO_4, and 1.5 ml of water. The mixture was stirred for 15 min, and the solution was poured into 300 ml of ice water. The brown precipitate was removed by filtration and washed with water to give 3 g (70%) of a fine crystalline precipitate with mp 140-141° (from ethanol). Found: C 48.4; H 4.4%. $C_9H_9N_3O_4$. Calculated: C 48.4; H 4.0%. UV spectrum (in ethanol), λ_{max}, nm (log ε): 223 (4.04), 327 (4.18). IR spectrum: 750-800 cm^{-1} (NO_2 group).

6,7-Dinitro-N-formyl-THQ (XVI). This compound was similarly obtained by refluxing 6,7-dinitro-THQ with excess formic acid. The brown needles had mp 163° (from ethanol). Found: C 47.6; H 3.5%. $C_{10}H_9N_3O_5$. Calculated: C 47.8; H 3.6%.

6,7-Dinitro-N-acetyl-THQ (XVII). This compound was similarly obtained as fine brown crystals with mp 155° (from ethanol). Found: C 49.8; H 4.0%. $C_{11}H_{11}N_3O_5$. Calculated: C 50.0; H 4.0%.

6,7-Dinitro-N-benzoyl-THQ (XVIII). This compound was similarly obtained as light-brown powder with mp 164° (from ethanol). Found: C 58.5; H 3.8%. $C_{16}H_{13}N_3O_6$. Calculated: 58.7; H 4.0%.

7-Nitro-N-acyl-THQ (VIII-XII). This compound was obtained by refluxing 5 g (0.027 mole) of 7-nitro-THQ with the appropriate acylating agent for 30 min. The solution was poured into 50 ml of water, and the resulting precipitate was removed by filtration and washed with water. The properties and results of analysis of VIII-XII are presented in Table 2.

5,7-Dinitro-N-chloroacetyl-THQ (XIX). A nitrating mixture consisting of 5 ml (0.01 mole) of nitric acid (sp. gr. 1.35) and 20 ml of concentrated H_2SO_4 was added with cooling to a solution of 1.4 g (0.005 mole) of 7-nitro-N-chloroacetyl-THQ in 40 ml of concentrated H_2SO_4, and the mixture was held at 0° for 3 h and then poured into 100 g of ice. The precipitate was removed by filtration and washed with water to give 1.3 g (78%) of a light-yellow finely crystalline powder with mp 113° (from ethanol). Found: C 44.3; H 3.4%. $C_{11}H_{10}ClN_3O_5$. Calculated: C 44.1; H 3.4%.

5,7-Dintitro-N-benzoyl-THQ (XX). This compound was similarly obtained from 1.4 g (0.005 mole) of 7-nitro-N-benzoyl-THQ. The yield of yellow precipitate with mp 175-176° (from ethanol) was 1.4 g (85%). Found: C 58.7; H 3.7%. $C_{16}H_{13}N_3O_5$. Calculated: C 58.7; H 4.0%.

5,7-Dinitro-THQ (VII). A. A 3-g (0.01 mole) sample of XIX was refluxed with 40 ml of concentrated HCl for 4 h. The hot solution was filtered, the mother liquid was cooled, and the resulting precipitate was removed by filtration to give 1.45 g (65%) of goldish-brown needles with mp 172-173° (from ethanol). Found: C 48.0; H 3.9; N 18.8%. $C_9H_9N_3O_4$. Calculated: C 48.4; H 4.0; N 18.8%. UV spectrum (in ethanol), λ_{max}, nm (log ε): 341 (3.92), 400 (4.09).

B. Similarly, 0.35 g (45%) of VII with mp 172-173° (from ethanol) was obtained from 1 g (6.3 mmole) of XX. The substance was chromatographically identical to that obtained by method A, and no melting-point depression was observed for a mixture of it and the product from method A.

5,7-Dinitro-N-formyl-THQ (XXI). This compound was similarly obtained from 5,7-dinitro-THQ as dark-yellow crystals with mp 93-94° (from ethanol). Found: C 47.5; H 3.6%. $C_{10}H_9N_3O_5$. Calculated: C 47.8; H 3.6%.

5,7-Dinitro-N-acetyl-THQ (XXII). This compound was obtained from 5,7-dinitro-THQ by the method used for the preparation of IX as bright-yellow needles with mp 133° (from ethanol). Found: C 49.9; H 4.1%. $C_{11}H_{11}N_3O_5$. Calculated: C 50.0; H 4.2%.

5,7-Dinitro-THQ (VII) and 7,8-Dinitro-THQ (XIII). A mixture of 10 ml (0.02 mole) of HNO_3 (sp. gr. 1.35) and 35 ml of concentrated H_2SO_4 was added dropwise with ice cooling to a solution of 0.01 mole of 7-nitro-N-acyl-THQ (VIII, IX, and XI) in 20 ml of concentrated H_2SO_4, and the resulting dark-red solution was cooled and stirred for another 15 min and then poured into 100 g of ice. The precipitate was removed by filtration and refluxed for 1 h with 25 ml of concentrated HCl.* The reaction mass was cooled and poured into water, and the aqueous mixture was made alkaline with ammonium hydroxide. The red precipitate of a mixture of 5,7- and 7,8-dinitro-THQ was removed by filtration and separated by preparative chromatography on activity III aluminum oxide (Brockmann scale) on 13 by 18 cm^2 plates in an ammonia-saturated chloroform system. The eluent was ethanol (Table 1). Compound VI was chromatographically identical to the product obtained above from XIX and XX, and no melting-point depression was observed for a mixture of these products. 7,8-Dinitro-THQ (XIII) was obtained as red needles with mp 120-121° (from ethanol). Found: C 48.1; H 4.6; N 18.8%. $C_9H_9N_3O_4$. Calculated: C 48.4; H 4.0; N 18.8%: UV spectrum (in ethanol), λ_{max}, nm (log ε): 234 (4.20), 358 (3.62), 434 (3.72).

The trend of the reactions and the purities of the compounds obtained were monitored by thin-layer ascending chromatography on a loose layer of activity II aluminum oxide (Brockmann scale) in an ammonia-saturated chloroform–benzene (3:1) system. The UV spectra of ethanol solutions were recorded with an SF-4A spectrometer. The NMR spectra were recorded from dimethyl sulfoxide and trifluoroacetic acid solutions with a Chart-60T spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The IR spectra of mineral oil suspensions were recorded with an IKS-22 spectrometer.

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*A 20% NaOH solution was used in the case of trifluoroacetyl derivative XI.