COMPOSITION OF THE PRODUCTS AND KINETICS OF THE ISOPROPYLATION OF 1,2,3,4-TETRAHYDROQUINOLINE IN SULFURIC ACID

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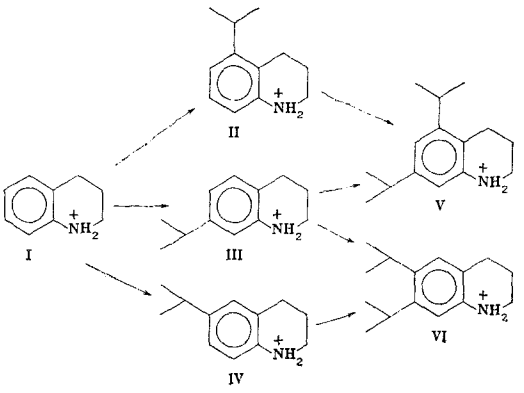
The kinetics of the alkylation of 1,2,3,4-tetrahydroquinoline with isopropyl alcohol in 90% sulfuric acid at 60°C were studied. It was established that the rate of alkylation in the 5 position is higher than for the corresponding position in the acyclic analog N,2-dimethylaniline; this was ascribed to the Mills–Nixon dynamic effect.

Little study has been devoted to the reactivity of the aromatic ring of 1,2,3,4-tetrahydroquinoline in electrophilic substitution processes, and the literature contains no quantitative data at all on the C alkylation of this system. The production of substituted tetrahydroquinolines opens up the possibility of simple syntheses of the corresponding substituted quinolines, which are often difficult to obtain. Moreover, a comparison of the reactivities of the tetrahydroquinoline system and its noncyclic analog N-methyl-o-toluidine is of theoretical interest. With this end in mind, in a continuation of our research on the isopropylation of arylammonium cations [1-3] we studied the kinetics of the alkylation of 1,2,3,4-tetrahydroquinoline with isopropyl alcohol in concentrated sulfuric acid.

The reaction was carried out under standard conditions [1-3]: at 60°C in 90% sulfuric acid containing 1.33 moles/liter isopropyl alcohol at a molar ratio of the substrate and isopropyl alcohol of 1:4. The conjugate acids of tetrahydroquinoline bases undergo alkylation in this medium [4].

We have previously shown that the reaction proceeds via Scheme 1 under such conditions.

Scheme 1



In the present research this scheme was proved by alternative syntheses of III and IV and by their identification with the reaction products by gas–liquid chromatography (GLC) and by the isolation of V and VI from the mixture of alkylation products with subsequent establishment of their structures by the usual methods. We do not have strong evidence for the presence of 5-isopropyl-1,2,3,4-tetrahydroquinoline (II) in the alkylation mixture, but considering that the number of theoretically possible monoisopropylation products is four and having genuine samples of 6-, 7-, and 8-isopropyltetrahydroquinolines at our disposal, we assigned the unidentified peak that appears on the chromatogram along with the other monoalkylation products to 5-isopropyl isomer II by the process of elimination.

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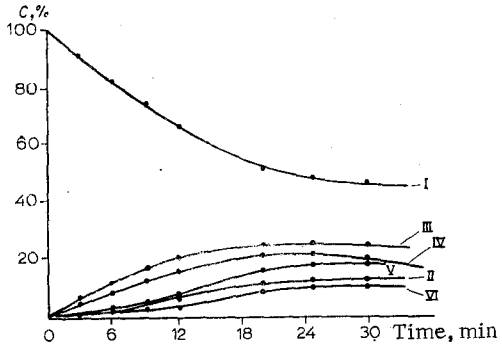


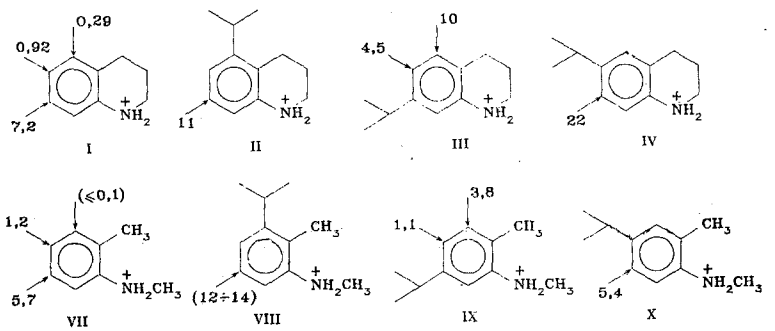
Fig. 1. Kinetics of the alkylation of 1,2,3,4-tetrahydroquinoline with isopropyl alcohol: I) substrate concentration; II-VI) concentrations of the alkylation products (the curves correspond to the calculated values, and the points correspond to the experimental values; for curves II and IV the scale along the axis of abscissas was increased by a factor of 10).

TABLE 1. Dependence of the Composition of the Products of Alkylation of 1,2,3,4-Tetrahydroquinoline on the Reaction Time

Time, min	Compound					
	I	II	III	IV	V	VI
3	92,9	0,05	6,1	0,5	0,3	0,2
6	86,0	0,1	10,9	0,9	1,3	0,6
9	77,6	0,3	15,5	1,2	3,5	1,8
12	70,8	0,6	18,0	1,5	6,0	3,0
20	48,8	1,1	23,0	2,2	16,4	8,4
25	48,6	1,4	21,0	1,9	17,5	9,4
30	47,1	1,2	22,2	1,7	18,4	9,1

As in [1-3], the course of the reaction was followed by means of GLC. The results are presented in Table 1. An analysis of these data based on the use of analog computer techniques [3] shows that each of the steps in the alkylation is described by second-order equations (first order in both the alcohol and the substrate). The calculated values of the rate constants ($\cdot 10^{-4}$ kg-mole^{-1}-sec^{-1}) and the corresponding values for noncyclic analogs, viz., N-methyl-o-toluidine derivatives [2], are presented in Scheme 2. It is apparent from Fig. 1 that the set of constants obtained describes the experimental data quite well.

Scheme 2



The rates of alkylation of the carbon atoms in the 6 and 7 positions in cation I do not differ substantially from those for noncyclic analog VII. However, I is also alkylated in the 5 position, whereas the analogous product (VIII) was not detected for noncyclic substrate

VII. This constitutes evidence either for its low rate of formation or for the extremely high rate of subsequent alkylation of VIII in the 5 position. The rate of isopropylation of substrate VIII in the 5 position was not determined directly, but it can be estimated by using data on the isopropylation of salts of o-toluidine [3] and its N-methyl derivative [2]. It follows from these values and from the data in [1] that under the indicated conditions the rate of reaction in the 5 position is lower by a factor of 2.5-3 when a methylammonium substituent is present than in the case of an unsubstituted ammonium group. This can be illustrated by comparison of the rate constant for alkylation in the 5 position of substrate VI (5.7) with the analogous value for the salt of o-toluidine (16.7) [3]. Since for the 3-isopropyl-2-methylanilinium cation the rate constant for substitution in the 5 position is $35 \cdot 10^{-4}$ kg-mole^{-1}-sec^{-1} [3], the corresponding value for VIII should then be on the order of $(12\text{-}14) \cdot 10^{-4}$ kg-mole^{-1}-sec^{-1}, which differs little from the value found in the present research for substitution of substrate II in the 7 position. It may therefore be asserted that the absence of a product of substitution in the 3 position of substrate VII is due precisely to its low rate of formation, the constant of which cannot exceed $0.1 \cdot 10^{-4}$ kg-mole^{-1}-sec^{-1} (if one takes into account the fact that the sensitivity of analysis by gas chromatography is no less than 0.3%). Thus we can state that the alkylation of cation I in the 5 position proceeds significantly more rapidly than in the analogous position of noncyclic analog VII. The same thing is apparent from a comparison of the corresponding rates of alkylation for substrates III and IX.

Numerous analogies of this effect for carbocyclic compounds are known in the literature. For example, the rates of acid-catalyzed hydrogen exchange (protodetritiation) [6] and sulfonation [7] of tetralin in the 5 position are higher by factors of three and two, respectively, than in the case of o-xylene. Such facts are usually discussed within the framework of the Mills–Nixon dynamic effect [8].

Let us note yet another peculiarity of substitution in the tetrahydroquinoline system. It is apparent from a comparison of the data for the III and IX structures, as well as the IV and X structures (see Scheme 2), that the presence of an isopropyl group in the 6 and 7 positions unexpectedly gives rise to an approximately fourfold increase in the activity of the adjacent (7 and 6, respectively) position as compared with the noncyclic analog. This fact is difficult to explain at the present time.

EXPERIMENTAL

The method used for the kinetic experiments was described in [1]. An LKhM-72 chromatograph with a flame-ionization detector and a 2 m × 4 mm steel column packed with 5% PEG 3000 on Chromosorb W (80-100 mesh) modified with 5% KOH was used; the carrier gas was helium, and the analysis temperature was 165°C. The calculations were carried out by internal normalization of the products of the heights of the peaks by the retention times. Each determination was repeated three times. The relative standard deviation was 5%. Mathematical modeling was carried out by means of an MN-10M analog computer as described in [3]. The PMR spectrum was recorded with a Tesla BS-467 spectrometer (60 MHz) with tetramethylsilane as the internal standard.

7-Isopropyl-1,2,3,4-tetrahydroquinoline (III). A fraction with bp 130°C (133 Pa) and d_4^{20} 0.9064 was isolated from the alkylation mixture by rectification with a column with an efficiency of ∿10 theoretical plates. The benzoyl derivative of this product had mp 70°C (hexane). Found: N 5.16%. $C_{19}H_{21}NO$. Calculated: N 5.02%. The same compound was obtained by alternative synthesis by the method in [9]. No melting-point depression was observed for a mixture of benzoyl derivatives of the two samples, and the latter had identical retention times.

8-Isopropyl-1,2,3,4-tetrahydroquinoline. This compound was obtained by condensation of 1.02 g (7.5 mmole) of o-isopropylaniline and 6.3 g (40 mmole) of 1-bromo-3-chloropropane by the method described in [10]. It was demonstrated by GLC that it was not present in the products of monoalkylation of tetrahydroquinoline.

6-Isopropyl-1,2,3,4-tetrahydroquinoline (IV). This compound was obtained by reduction of 6-isopropylquinoline with tin in 37% hydrochloric acid by the method in [11]. The presence of 6-isopropyl-1,2,3,4-tetrahydroquinoline in the monoalkylation products was confirmed by GLC.

5,7-Diisopropyl-1,2,3,4-tetrahydroquinoline (V). This compound was isolated from the alkylation mixture by rectification with a column with an efficiency of 10 theoretical plates. The product had bp 147°C (133 Pa), d_4^{20} 0.9736, and n_D^{20} 1.550. The benzoyl derivative had mp 132.5-133°C (hexane). Found: N 4.5%. $C_{22}H_{27}NO$. Calculated: N 4.52%. The structure of V was proved by conversion to 8,10-diisopropyl-2,3,6,7-tetrahydro-1H,5H-benzo[i,j]quinolizine, which was described in [12].

6,7-Diisopropyl-1,2,3,4-tetrahydroquinoline (VI). This compound was isolated from the fraction of the products of dialkylation of 1,2,3,4-tetrahydroquinoline by means of TLC on a loose layer of activity II (Brockmann) aluminum oxide in a hexane–diethyl ether system (10:1). The PMR spectrum in the region of aromatic protons consisted of two one-proton singlets with δ 6.23 and 6.00 ppm. The absence of spin–spin coupling indicates that the 5 and 8 positions remained unsubstituted.

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