ISOPROPYLATION OF INDOLINE

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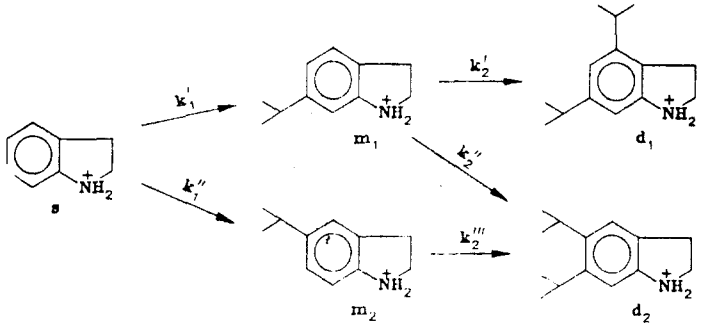
The composition of the reaction products was ascertained, and the kinetics of the alkylation of indoline with isopropyl alcohol in 90% sulfuric acid at 60°C were studied. The reactivities of indoline and its carbocyclic analogs are compared.

The facile conversion of indole to indoline and vice versa has made it possible to develop a method for the introduction of a substituent into its carbocyclic fragment [1, 2]. However, little study has been devoted to the reactivity of indoline in electrophilic substitution processes, and no data at all on the C-alkylation of this system are available.

In our current research we investigated the conditions for the isopropylation of indoline with isopropyl alcohol in aqueous sulfuric acid, ascertained the composition of the reaction products, and measured the rates of the mono- and disubstitution steps. It was established by GLC, NMR spectroscopy, and alternative syntheses that the reaction proceeds via the following scheme:



The structure of 6-isopropylindoline was proved by its dehydrogenation by means of chloranil to the previously described 6-isopropylindole [3]. The identification of the structure of the second monoisopropylindoline as the 5-substituted isomer was proved by its PMR spectrum. Two one-proton doublets at 6.8 and 6.4 ppm (AB system, J = 7.5 Hz) and a singlet at 6.3 ppm are observed in the aromatic-proton energy.

The structure of 4,6-diisopropylindoline was proved by dehydrogenation to 4,6-diisopropylindole and alternative synthesis of the latter by cyclization of the formyl derivative of 2-methyl-3,5-diisopropylaniline in analogy with the known method [4]. The PMR spectrum of the second diisopropylindoline in the aromatic-proton region is also represented by two one-proton singlets at 6.28 and 7.67 ppm; in accordance with the exclusion principle, this can correspond only to 5,6-diisopropylindoline.

The kinetics of the process were studied under standard conditions [5] at 60°C in a medium containing 1.33 moles of isopropyl alcohol per liter of 90% sulfuric acid. The composition of the reactions masses and the dynamics of its change were determined by GLC. The kinetic curves are presented in Fig. 1. Analog computer technology was used to find the rate constants.

The partial rate constants ($\cdot 10^{-4}$ kg·mole^{-1}·sec^{-1}) are presented in the scheme, in which they are compared with the analogous values for structurally similar carbocyclic compounds — salts of N-methyl-o-toluidine and its C-isopropyl-substituted derivatives [6]:

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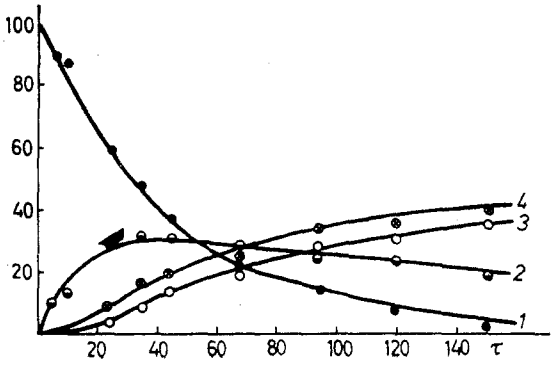
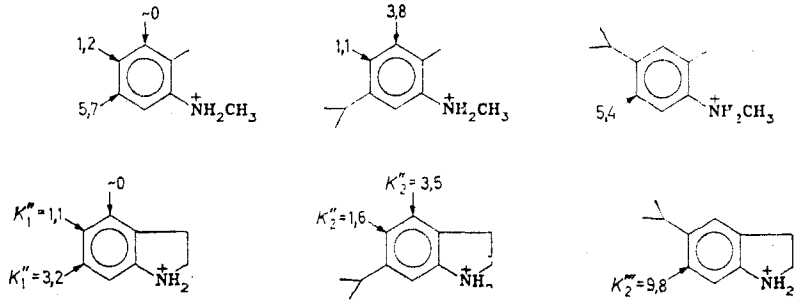


Fig. 1. Alkylation of indoline with isopropyl alcohol in 90% H_2SO_4 at 60°C (the curves were calculated, while the points are the experimental values): 1) indoline; 2) sum of the 5- and 6-isopropylindolines; 3) 4,6-diisopropylindoline; 4) diisopropylindoline.



It is apparent that substantial specific effects of the heterocyclic fragment in the reactivity of the aromatic ring are absent. In this respect this compound differs from 1,2,3,4-tetrahydroquinoline, in which specific effects of the condensed hydrogenated heterocyclic ring on the reactivity of the aromatic fragment are manifested quite distinctly [7]. The increased reactivity of the 5 position in 1,2,3,4-tetrahydroquinoline was previously interpreted in the spirit of the Mills—Nixon effect. Considering the results of our research, it seems more likely that the indicated effect of the six-membered heteroatomic ring is due to the nonplanarity of the molecule.

EXPERIMENTAL

The method used to carry out the kinetic experiments was described in [5]. We used an LKhM-72 chromatograph with a flame-ionization detector and a steel column (2 m × 4 mm) packed with 5% SE-30 on Chromosorb W (80-100 mesh); the carrier gas was helium, and the analysis temperature was 175°C. The calculations were made by internal normalization of the products of multiplication of the peak heights by the retention times. Each determination was repeated three times. The relative standard deviation was 5%. Mathematical modeling was carried out using an analog computer as described in [6]. The PMR spectrum was recorded with a Tesla BS-467 spectrometer (60 MHz).

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

5-Isopropylindoline. This compound was isolated by column chromatography of the fraction of monoalkylation products on Silpearl silica gel with hexane—chloroform—acetone (1:4:2) as the eluent. PMR spectrum (CCl_4, TMS): 1.14 (6H, d, CH_3), 2.4-2.9 (1H, m, CH), 2.87 (2H, t, CH_2N), 3.33 (2H, t, CH_2C), 6.4-6.8 ppm (3H, m, Ar).

6-Isopropylindoline ($C_{11}H_{15}N$). This compound was isolated by fractionation of the mixture and had bp 89°C (400 Pa). The acetyl derivative had mp 113.5-114.5°C, and the hydrochloride had mp 119-121°C.

The same compound was obtained by alternative synthesis by the method in [3]. The two samples had identical retention times.

4,6-diisopropylindoline. This compound was isolated from the fraction of dialkylation products and had bp 100-102°C (400 Pa), with subsequent purification by fractional crystallization of the hydrochlorides. The acetyl

derivative had mp 195-196°C. PMR spectrum [d_6-DMSO, hexamethyldisiloxane (HMDS)]: 1.0 (12H, d, CH_3), 2.4-3.33 (4H, t, CH_2; 2H, m, CH), 6.34 (1H, s, 5-H), 6.86 ppm (1H, s, 7-H).

5,6-Diisopropylindoline. This compound was isolated from the fraction of dialkylation products and had bp 105-107°C (400 Pa). The hydrochloride had mp 260-262°C. PMR spectrum (CCl_4, TMS), 1.08 (12H, d, CH_3), 2.6-3.63 (4H, t, CH_3; 2H, m, CH), 6.28 (1H, s, 4-H), 7.67 ppm (1H, s, 7-H).

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