**7-Ethoxy-5,6-dihydropyrazolo[3,4-f]quinoline** (XIII, $C_{12}H_{12}N_2O_2$). A solution of 2.46 g (0.01 mole) of the enamine (IXb) and 1.04 g (0.015 mole) of hydrazine hydrate in 20 ml of absolute ethanol was stirred for 1 h, evaporated, the oil triturated with 2-propanol, and 1.2 g (56%) of the pyrazoloquinoline (XIII) filtered off. Mp 144.5-145.5°C, $M^{+\cdot}$ 215.

**7-Ethoxy-5,6-dihydrooxazolo[5,4-f]quinoline** (XIV, $C_{12}H_{12}N_2O_2$). A solution of 2.46 g (0.01 mole) of the enamine (IXb) and 1.04 g of hydroxylamine hydrochloride in 10 ml of glacial acetic acid was boiled for 3.5 h with the addition of 1-2 drops of concentrated sulfuric acid, evaporated, and passed through a column (silica gel 40/100, ethyl acetate). The first fraction contained 0.82 g (38%) of the isoxazolinone (XIV), mp 93.5-94°C, $M^{+\cdot}$ 216.

**5-Ethyl-6-oxo-4,5,7,8-tetrahydropyrazolo[3,4-f]quinoline** (XV, $C_{12}H_{13}N_3O$) was obtained as described for (XIII) from the enamine (Xb), but the reaction mixture was kept for 3 days, evaporated, the oil rubbed with 2 ml of ethyl acetate, and the pyrazoloquinoline (XV) filtered off (1.81 g, 84%), mp 248-253°C, $M^+$ 215.

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# PMR SPECTROSCOPIC STUDY OF THE KINETICS OF H/D EXCHANGE IN METHYL GROUPS IN A SERIES OF HETEROCYCLIC AZINES


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UDC 543.422.25:541.124'-127:547.823'854.04



*The rate of H/D exchange among methyl group protons in a series of substituted 3-hydroxypyridines, 5-hydroxypyrimidines, and their N-oxides has been shown to increase with increasing acidity of the medium. The most reactive form of these molecules is the cationic form at pH < 2. The rate of H/D exchange of $CH_3$ group protons in 3-hydroxypyridine derivatives has also been found to be several orders of magnitude lower than the rates of exchange for methyl-substituted 5-hydroxypyrimidine and its N-oxide. Effective rate constants for methyl group proton exchange have been estimated. In the case of methyl-substituted 5-hydroxypyrimidine N-oxide derivatives it has been established that the rate of proton exchange is greater for an ortho-methyl group than for a methyl group in the para-position relative to the N-oxide site.*


Nitrogen heterocycles (such as β-hydroxypyridine and pyrimidine derivatives, for instance) serve as the basis for the synthesis of many pharmaceutical agents. Studies of the characteristic reactivity of side chain protons in series of substituted


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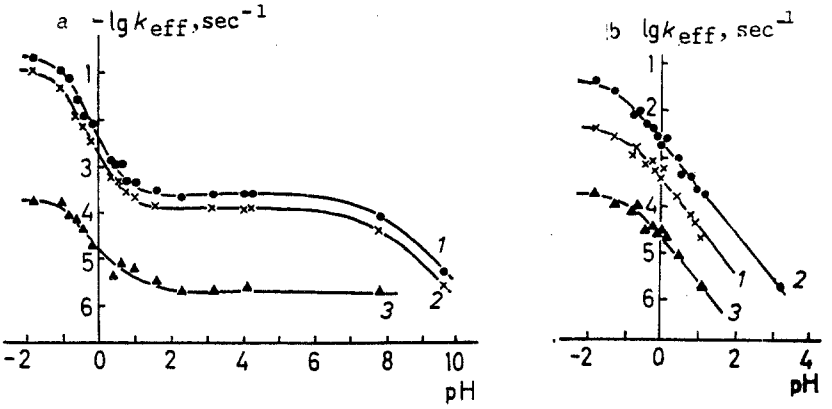



Fig. 1. Relationship between the rate ($k_{eff}$) of H/D exchange for the $CH_3$ group protons in 2,4,6-trimethyl-5-hydroxypyrimidine (a) and 2,4,6-trimethyl-5-hydroxypyrimidine-1-oxide (b) and the pH value of the medium at 90°C: 1) 4-$CH_3$ group; 2) 6-$CH_3$ group; 3) 2-$CH_3$ group.

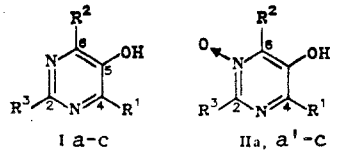
TABLE 1. Effective Rate Constants for H/D Exchange among $CH_3$ Group Protons in a Series of Methyl-Substituted 5-Hydroxypyrimidines and Their N-Oxides at pH 0 and 90°C

| Compound | n* | $k_{eff}$, $sec^{-1}$ | Compound | n* | $k_{eff}$, $sec^{-1}$ |
|---|---|---|---|---|---|
| Ia | 4 | $4{,}70 \cdot 10^{-3}$ | IIa | 4 | $1{,}91 \cdot 10^{-4}$ |
| Ib | 4 | $8{,}82 \cdot 10^{-4}$ | IIa' | 6 | $7{,}08 \cdot 10^{-4}$ |
| | 6 | $4{,}41 \cdot 10^{-4}$ | IIb | 4 | $2{,}95 \cdot 10^{-5}$ |
| Ic | 2 | $1{,}78 \cdot 10^{-5}$ | | 6 | $3{,}16 \cdot 10^{-4}$ |
| | 4 | $4{,}47 \cdot 10^{-3}$ | IIc | 2 | $2{,}43 \cdot 10^{-5}$ |
| | 6 | $2{,}23 \cdot 10^{-3}$ | | 4 | $3{,}80 \cdot 10^{-4}$ |
| | | | | 6 | $2{,}10 \cdot 10^{-3}$ |

*n) position of the $CH_3$ group in the ring.

azines and their N-oxides are of interest in this regard for the development of optimal conditions for the introduction of functional substituents in the heterocycles or their side chains. We have previously [1-4] investigated the kinetic principles and mechanism of H/D exchange for the hydrogen atoms in 3-hydroxypyridine, 5-hydroxypyrimidine (I), and their N-oxides (II). It has been found that substitution of the reactive ring positions in 3-hydroxypyridine and compound I occurs via an $S_{E2}$ mechanism, and that the most reactive forms of these molecules are their anionic (a) and neutral (N) forms. In the case of compounds IIa, a'-f, their reactivity depends on the reaction conditions and can proceed both via an $S_{E2}$ mechanism as well as via direct nucleophilic attack of an $OD^-$ ion via carbanion formation ($S_{E1}$).

In the present paper we have studied the characteristics of H/D exchange among side chain methyl group protons in a series of substituted 3-hydroxypyridines, compounds Ia-c, IIa, a'-c at 90 and 160 °C in the pD range 0-10 and $H_0$ 0 to –2.



I a-c IIa, a'-c

I, II a $R^1=CH_3$, $R^2=R^3=H$; b $R^1=R^2=CH_3$, $R^3=H$; c $R^1=R^2=R^3=CH_3$; II a' $R^1=R^3=H$, $R^2=CH_3$

The kinetics of $CH_3$ group hydrogen isotope exchange can be expressed satisfactorily using a pseudo-first-order rate equation relative to starting material [5]. Effective rate constants for deuterium exchange ($k_{eff}$) at various medium pH (or $H_0$) val-

ues were estimated according to a literature method [6]. The rate constants for H/D exchange among the methyl group protons in compounds I and II have been determined in the system $D_2SO_4/D_2O$ at pH 0 and 90°C (Table 1), and graphs showing the pH dependence of $k_{eff}$ have been constructed for each of the reactive methyl groups in compounds Ic and IIc at 90°C (Figs. 1 and 2). Comparison of the results obtained for compounds I and II reveals that H/D hydrogen exchange in every methyl group occurs sequentially in the order $CH_3 \rightarrow CH_2D \rightarrow CHD_2 \rightarrow CD_3$. As the acidity of the medium is increased, the rate of isotope exchange for the $CH_3$ group hydrogen atoms also increases. For most of the heterocycles examined in this study the rate of the exchange reaction at pH > 2 is two or more orders of magnitude slower than the exchange rate for the corresponding $CH_3$ group protons at higher medium acidity values (cf. Fig. 1). The rates of H/D exchange are different for the $CH_3$ group protons in compounds I and II. In the range pH < 2 all of the $CH_3$ groups are reactive. Molecule Ic contains three methyl groups. In aqueous solution the following equilibrium forms are possible, depending on the acidity of the medium: the cationic form (C), N and A [7]. In this pH (and $H_0$) interval protonation occurs at only nitrogen atom ($pK_a = 3.8$ [7]). In the range pH < 3 form C predominates in solution and, consequently, the H/D exchange reaction for the methyl group protons proceeds predominantly in the cationic form of the molecule. Estimates of $k_{eff}$ for the $CH_3$ group protons in the 4- and 6-positions in the ring in compounds Ib, c were made in the same manner as for compound I [3]. Our conclusion that for compound Ic the rate of the H/D exchange reaction for the 4-$CH_3$ protons is greater than for the 6-$CH_3$ protons follows from comparison with the value of $k_{eff}$ for the methyl group in compound I (cf. Table 1). It has previously been demonstrated [7] that for compound Ia the first protonation site is the N(1) atom; consequently, for compound I the para-position relative to the protonated nitrogen atom appears to be more reactive. This is further confirmed by existing literature data for H/D exchange among methyl group protons in substituted pyridines and pyrimidines [8].

Analysis of the isotopic exchange data for methyl-substituted 3-hydroxypyridine derivatives has also indicated that substitution of the methyl group protons is not observed upon heating (90°C, more than 100 h). For this reason we conclude that the rate of hydrogen exchange for the $CH_3$ groups in these derivatives is several orders of magnitude slower than the rate of hydrogen exchange for the $CH_3$ groups in compounds Ia-c.

In molecule IIc all three methyl groups are nonequivalent. In the acidity range pH < 2 the compound exists predominantly in its C form, since the first protonation site in the N-oxide IIc should be the oxygen atom in the N–O group, according to the literature [9]. The effective rate constant for H/D exchange for the 6-$CH_3$ group protons, which are located ortho- to the cationic center, is thus substantially greater than for the protons in the 4-$CH_3$ and 2-$CH_3$ positions. Analogous results have been obtained for compounds IIa and IIb as well. The reactivity of the methyl groups increases in the order 6-$CH_3$ > 4-$CH_3$ > 2-$CH_3$.

As in the case of the methyl-substituted 3-hydroxypyridine derivatives the rate of H/D exchange for the methyl groups in 3-hydroxy N-oxide derivatives is several orders of magnitude slower than the exchange rates for compounds IIa, a'-c.

Heating these compounds to 90°C for over a course of 150 h at pH > 0 did not lead to the formation of deuterium-substituted compounds. The onset of deuterium exchange for the 6-$CH_3$ and 4-$CH_3$ group protons was observed only after heating for more than 100 h at a solution acidity value $H_0 = -1.5$.

It should also be noted that when the H/D exchange reaction was carried out at 90°C no significant amount of ring hydrogen atom substitution was observed for any of the compounds examined in this study. However, as the temperature was raised the rates of methyl group proton exchange as well as ring proton exchange both increased (Fig. 2). At 160°C H/D exchange was also observed for the methyl group protons in 3-hydroxypyridines. Thus, for example, in the case of 2-methyl-3-hydroxypyridine (pH 1, 160°C) $k_{eff} = 5.5 \cdot 10^{-5}$ $sec^{-1}$; under the same conditions for Ia, $k_{eff} = 1.2 \cdot 10^{-3}$ $sec^{-1}$, i.e., almost two orders of magnitude lower than for the methyl-substituted analog compound I.

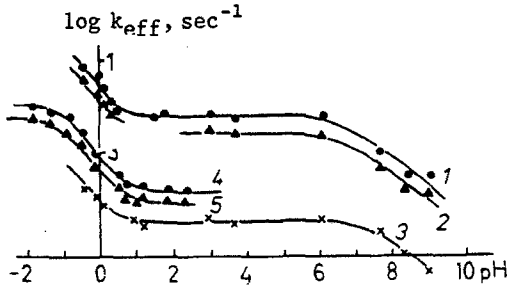



Fig. 2. Relationship between the rate ($k_{eff}$) of H/D proton exchange in 4,6-dimethyl-5-hydroxypyrimidine and the pH value of the medium for the exchange reaction at 160 (1-3) and 90°C (4, 5): 1) 4-$CH_3$ group; 2) 6-$CH_3$ group; 3) 2-H; 4) 4-$CH_3$ group; 5) 6-$CH_3$ group.

Comparison of the results of this study of the kinetic behavior or principles of H/D exchange for $CH_3$ group protons in these series of β-hydroxy heterocyclic azines and their N-oxides demonstrates that the rate of hydrogen isotope exchange increases as the acidity of the medium is increased, namely, that the C form is the most reactive form of these molecules; the fastest reaction rates are observed at pH < 2. The ease or facility of engagement of $CH_3$ group protons in H/D exchange in derivatives of compound I and its N-oxide IIa, a'-c varies in the series (relative to the cationic site) γ-$CH_3$-I > α-$CH_3$-I; α-$CH_3$-II > γ-$CH_3$-II. The activity of C–H bonds in $CH_3$ groups thus decreases in the sequence $\overset{+}{N}H \lessgtr \overset{+}{N}–OH > N \lessgtr \overset{+}{N}–\overset{-}{O} \gg CH_{arom}$. The rate of $CH_3$ group H/D exchange in monoazines is also several orders of magnitude lower than the rate of exchange in diazines. H/D exchange reactions most likely proceed via intermediate carbanion formation after proton abstraction from a $CH_3$ group, or as a result of ketimide-enamine tautomerism [10], in which carbanion formation is stabilized as a consequence of intramolecular rearrangement of the molecular structure.

The ease of $CH_3$ group proton engagement in this type of exchange reaction is governed or determined by the π-electron density on the methyl group carbon atom; the presence of a positive charge on the ring nitrogen atom (form C) therefore significantly reduces the π-electron density in the ring and on the methyl carbon atom, thus facilitating proton abstraction from the $CH_3$ group protons. For the N forms of these molecules the C–H bond proton activity or mobility is lower, and the rate of H/D exchange is diminished, while for their A forms exchange occurs only under extremely harsh conditions; the sharp drop in the rate of exchange in this case can be attributed to a large degree to the enhanced electron density in the ring upon ionization of the hydroxyl group at high solution pH values [7, 9].

It is interesting to note as well that the rate of H/D exchange for the $CH_3$ group protons in compounds Ia-c and IIa, a'-c correlates with the chemical shift differences for the $CH_3$ group protons in the C and N forms, respectively, $\Delta\delta_{C-N}$ [7, 9], which reflects the change in electron density at the ring and methyl substituent carbon atoms upon protonation. $\Delta\delta_{C-N}$ for derivatives Ia, b is higher than for compounds IIa, b. Thus, for example, $\Delta\delta_{C-N} = 0.27$ (for Ia), 0.15 (for IIa), and 0.18 (for IIa'); $k_{eff} = 4.7 \cdot 10^{-3}$ (for Ia), $1.91 \cdot 10^{-4}$ (for IIa), and $7.08 \cdot 10^{-4}$ $sec^{-1}$ (for IIa') (at pH 0 and 90°C).

## EXPERIMENTAL

Compounds I and II were synthesized and purified according to literature methods [11, 12]. Samples were prepared in the form of 0.2 mmole/liter solutions in $D_2O$. The acidity value in the range pH 0-10 was varied by the addition of small amounts of 98% $D_2SO_4$ or 1 N NaOD to a flask containing the sample. Solution pH values were measured on a universal ÉV-74 ion meter with a glass electrode ESL 63-07 with an accuracy of ±0.05 pH units. Solutions at predetermined $H_0$ values were prepared according to a literature procedure [13]. PMR spectra were recorded on a Varian HA-100 spectrometer at 26°C. The procedures for sample preparation and the kinetic experiments have been published previously [1]. The course of H/D exchange was monitored by PMR. The degree of isotropic exchange was determined by comparison of the relative areas of a control signal for the $CH_3$ group protons in tetramethylammonium iodide, which was added to the sample solution, and the signal area of the $CH_3$ group proton signal undergoing exchange.

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# DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN BRIDGEHEAD POSITIONS

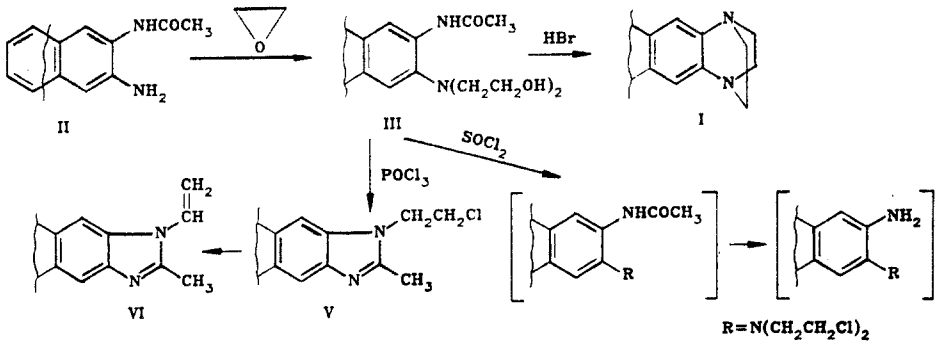
## 20.* SYNTHESIS OF NAPHTHO[2,3-b]-1,4-DIAZABICYCLO[2.2.2]OCTENE

**E. N. Kuznetsova and G. C. Shishkin**

UDC 547.864:543.422

*Reaction of 2-acetamido-3-bis(2-hydroxyethyl)aminonaphthalene with phosphorus oxychloride leads to the formation of 2-methyl-1-(2-chloroethyl)naphtho[2,3-d]imidazole, while reaction with hydrobromic acid gives naphtho[2,3-b]-1,4-diazabicyclo[2.2.2]octane in 13% yield. The yield of the latter can be increased to 45% by exchange of the hydroxyl groups in the starting material by chlorine and by deacetylation.*

Continuing our studies of 1,4-diazabicyclic systems containing annelated aromatic rings, we have carried out the synthesis of naphtho[2,3-b]-1,4-diazabicyclo[2.2.2]octene (I) according to a scheme developed previously [2] for the synthesis of benzo[b]-1,4-diazabicyclo[2.2.2]octene:




Upon monoacetylation of 2,3-diaminonaphthalene we observed the formation of a multicomponent mixture, the composition of which was altered after recrystallization. Using TLC analysis we were able to select conditions for achieving a max-

*For Communication 19, see [1].

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