INVESTIGATION OF ACID DEUTERIUM EXCHANGE IN
A NUMBER OF ISOQUINOLINE AND 4-HYDROXY-
ISOQUINOLINE DERIVATIVES

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The acid deuterium exchange of isoquinoline and 4-hydroxy- and 3-methyl-4-hydroxyiso-
quinolines at 145°C in 94% D₂SO₄ was investigated by PMR spectroscopy. The sequence
of substitution and the rate constants for deuterium exchange of the protons of the iso-
quiline ring were determined. The most reactive protons in isoquinoline and 3-methyl-
4-hydroxyisoquinoline are those of the benzene ring, while the proton in the 3 position of
the β-pyridol ring is the most reactive in 4-hydroxyisoquinoline.

A PMR spectroscopic investigation of the basic deuterium exchange of 3-hydroxyquinoline [I] and 4-
hydroxyisoquinoline [I] demonstrated that the introduction of an annelated benzene ring into the 5,6 or 4,5
positions of the β-pyridol ring has a different effect on the sequence of substitution and the reactivity of
the heteroring protons. Thus, in contrast to 3-hydroxyppyrindine [2], the proton in the 4 position was prima-
arily exchanged in the basic deuterium exchange of 3-hydroxyquinoline. On the other hand, the same se-
quence of substitution as in 3-hydroxyppyrindine was retained in the case of 4-hydroxyisoquinoline, but the
rate of exchange of the ortho proton was higher by a factor of 100.

In connection with the data presented, it seemed of great interest to compare the chemical behavior
of 3-hydroxyquinoline, 4-hydroxyisoquinoline, and their derivatives during acid deuterium exchange.

The acid deuterium exchange of isoquinoline and 4-hydroxy- and 3-methyl-4-hydroxyisoquinolines
was investigated in the present paper by PMR spectroscopy.

ISOQUINOLINE

The interpretation of the PMR spectrum of isoquinoline is simplified by the fact that there is no dif-
ficulty in isolating the signals from the pyridine ring protons from the overall spectrum. Thus the 1-H
signal lies in the weakest-field region at 9.41 ppm and is a singlet. The 3-H and 4-H chemical shifts prac-
tically coincide (8.34 ppm), and one signal, the intensity of which corresponds to two protons, is observed
in the spectrum. The signals from the protons of the benzene ring give a more complex pattern of over-
lapped multiplets at 7.90-8.40 ppm. On the basis of our experimental results and an analysis of the litera-
ture data, the sequence of arrangement of the chemical shifts of these protons varies in the following order:
8-H, 5-H, 7-H, 6-H.
The order of substitution of the isoquinoline protons in our experiments (94% D₂SO₄, 145°) coincides with the literature data [3] for deuterium exchange in 90% D₂SO₄ at 180°. The 5-H proton initially undergoes exchange, followed by the 8-H proton; the total exchange of 8-H is complete 27 h after the instant the kinetic experiment is set up. Changes accompanied by the appearance of a singlet in the region of the 7-H signal are observed in the portion of the spectrum from the 7- and 6-H protons after heating for 6 h; this is evidence that the 6-H proton enters into deuterium exchange. As heating is continued, the intensity of the singlet increases, and exchange of 6-H is complete after 70 h. Exchange of the protons of the pyridine ring was not observed during the experiments.

4-Hydroxyisoquinoline

The signal from the NH proton is in the weakest-field region at 12.6 ppm. The signal of the 1-H proton (8.95 ppm) (see Fig. 1) is a singlet, upon which is superimposed a doublet caused by spin-spin coupling (J = 8.0 Hz) with the 3-H proton. The NH signal vanishes on even slight heating because of complete exchange by deuterium, and the 1-H signal is converted to a singlet. A group of signals of the remaining ring protons is situated at stronger field at 7.30–8.50 ppm, and there is no difficulty in isolating the 3-H singlet signal at 7.95 ppm. Since the assignment of the benzene ring signals is obvious, there is a possibility for the direct observation of deuterium exchange. The multiplet of the 8-H proton, which is due to coupling with 7- and 6-H, lies at 8.30 ppm. The multiplet of the 5-H proton, which couples with 6-H and 7-H, is partially superimposed on it. The 7- and 6-H protons give signals at 7.99 and 8.14 ppm, and their multiplicity is due to coupling with 8-, 6-, and 5-H and 5-, 7-, and 8-H, respectively. The 3-H proton is practically completely exchanged even after heating for 15 min. In addition, there are changes in the 5-H region of the spectrum. Further heating leads to a change in the spectrum both in the region of the 5- and 8-H protons and that of the 7- and 6-H protons, as evidenced by the development of doublets from the latter protons as 5- and 8-H are substituted (curve b). Heating for 8 h sharply changes the spectral pattern (curve c). Exchange of 5-H and 8-H is complete by this time, and the degree of substitution of 6-H is sufficient to be reflected in the character of the spectrum. In fact, in addition to the two doublets from 7-H and 6-H, a singlet in the 7-H region from a structure with a substituted 6 position is clearly seen. The intensity of the singlet increases on further heating, while the intensity of the 8-H doublet falls, and 6-H exchange is complete after 45 h (curve d). The rates of exchange of the protons that participate in the reaction were estimated from the change in the ratio of the areas of the 1-H signal (which does not undergo exchange) and the signal of the proton under consideration. We made a detailed examination of the calculation of the exchange rate constants in a previous communication [4]. The rate constants calculated in this way were as follows: k₃ = 1.3 · 10⁻², k₄ = 1.0 · 10⁻², k₅ = 2 · 10⁻³, and k₆ = 2.1 · 10⁻⁴ min⁻¹. In this case, the 1-H and 7-H protons do not participate in the exchange. Thus the introduction of a hydroxyl group into the pyridine ring of isoquinoline activates the 5, 6, and 8 positions of the ring. In addition, in the case of 4-hydroxyisoquinoline, the a proton of the β-pyridol ring is the first to undergo exchange; this was not the case in isoquinoline itself or in 3-hydroxypyridine. A comparison of the experimental data on the acid exchange of 3-hydroxypyridine and 4-hydroxyisoquinoline attests to the fact that the introduction of an anelated benzene ring into the 4,5 positions of the β-pyridol ring considerably increases the reactivity of the proton in the ortho position relative to the hydroxyl group. An analysis of the results of the acid and basic deuterium exchange of 4-hydroxyisoquinoline indicates a different sequence of substitution and different reactivities of the protons of the isoquinoline ring for these two cases. Thus, in the case of basic exchange, both positions of the β-pyridol ring are most reactive, and the protons of the benzene portion of the molecule do not participate in the exchange. However, in acid exchange, the 5-, 8-, and 6-H protons of the benzene ring participate along with the 3-H proton of the β-pyridol ring.