STERICALLY HINDERED 3-PYRIDINOLS
COMMUNICATION 5. STUDY OF THE COURSE OF AMINOMETHYLATION
AND HYDROXYMETHYLATION REACTIONS IN THE 2-ALKYL-3-PYRIDINOL SERIES
WITH THE AID OF PROTON MAGNETIC RESONANCE AND OF CHEMICAL METHODS

(UDC 547.82 + 542.91)

L. D. Smirnov, V. P. Lezina, V. F. Bystrov, and K. M. Dyumaev

Institute of Chemical Physics, Academy of Sciences, USSR
Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 10,
pp. 1836-1845, October, 1965
Original article submitted July 11, 1963

The aminomethylation and hydroxymethylation of 3-pyridinols not only present great theoretical interest,
but also open up the way for the synthesis of substances close in structure to vitamin B₆ and are therefore very valu-
able from the biological point of view. As we supposed earlier [1], the Mannich bases prepared from 3-pyridinols,
and also their transformation products (alkyl [2, 3] and hydroxymethyl [2] derivatives), show a wide range of im-
portant chemical and biological properties. They are able to inhibit free-radical processes [4], they show B₆ vita-
mamin activity, and they have both antitumor and radiation-protective properties: individual members can save up
to 65% of animals which have received a lethal dose of ionizing radiation [5]. A particularly noteworthy property
found in compounds of this class is antivitamin activity with respect to inositol and pantothenic acid [6].

Fig. 1. PMR spectra of: a) (IIIA) in D₂O; b) (IIIB) in D₂O;
c) (IIIC) in CHCl₃ (for denotation see Table 1).
We have shown [1] that in the 2,6-dialkyl-3-pyridinol series 4-aminomethylation can readily be effected, which, of course, opened up the possibility, in principle, of the 4-substitution of 3-pyridinols in general. The few data in the literature have concerned only α-substitution in such reactions with various 3-pyridinols. It has thus been shown that in the case of 3-pyridinol [7] and 6-methyl-3-pyridinol [8] amino- and hydroxy-methylation are directed into the 2-position of the pyridine nucleus. The only attempt to prepare the 4-aminomethyl and 4-hydroxymethyl derivatives of 5-hydroxy-6-methyl-3-pyridinemethanol [9] was unsuccessful.

We here report an investigation of the possibility of effecting these reactions with 2-methyl-3-pyridinol because a number of authors have not been able either to bring about 4-substitution and isolate the products in the pure state or to establish the structure of the aminomethyl and hydroxymethyl derivatives. We also considered it desirable to establish the relative reactivities of the free α- and γ-positions in the amino- and hydroxy-methylation of 2-alkyl-3-pyridinols. It is known that for some related compounds calculation by the molecular orbital method shows that the behaviors of the two reaction centers can be expected to be different, so that substitution may go in stages. We indeed observed the expected difference in reactivity between the 4- and 6-positions of 2-methyl-3-pyridinol, and it is well illustrated by the following facts.

In the 6-position the Mannich reaction goes quantitatively with stoichiometric proportions of components, and it is accompanied by the liberation of heat; hydroxymethylation goes in the 6-position in 60% yield. Aminomethylation in the 4-position goes only after the occupation of the free α-position, and an excess of reagents and the application of heat are necessary. We did not observe the occurrence of hydroxymethylation in the 4-position. Hence, depending on the reaction conditions and proportions of reactants, we were able to bring about reaction in the desired direction, which enabled us to develop methods for the preparation of both 2-alkyl-6-(aminomethyl) [or hydroxymethyl]-3-pyridinols and 2-alkyl-4,6-bis(dialkylaminomethyl)-3-pyridinols.

The aminomethylation of 2-methyl-3-pyridinol (II) with formaldehyde and dimethylamine or piperidine goes smoothly with formation first of mono- and then bis-(substituted amino)methyl derivatives. In an attempt to carry out this reaction with diethylamine, both with 2,6-dialkyl- and with 2-alkyl-3-pyridinols, we did not succeed in obtaining the corresponding 4-substituted products. It appears that here an anomaly is occurring which we have mentioned several times previously [10], and the possibility cannot be excluded that the fact that diethylamine was used in the Mannich reaction was the cause of the lack of success in the case of 5-hydroxy-6-methyl-3-pyridinemethanol [9].

When boiled with acetic anhydride 4,6-bis(dimethylaminomethyl)-2-methyl-3-pyridinol readily gave 5-hydroxy-6-methyl-2,4-pyridinedimethanol triacetate (IX). Hydrolysis of this compound led to the formation of a new isomer of pyridoxine-5-hydroxy-6-methyl-2,4-pyridinedimethanol (X).

The PMR spectra of the compounds (III) (see scheme), prepared by monoaminomethylation, are given in Fig. 1. These compounds give characteristic signals from the α-CH₃ group in the range 1.5-2.5 p. p. m., from the methylene group at 3.6-3.7 p. p. m., and from the protons of the pyridine ring at 6.6-7.8 p. p. m. * The signals from N-alkyl groups enable us to determine the structure of the substituent on the basis of the following peculiar

* The assignment of the signals was made on the basis of our previous work [1, 2] and data in the literature [11].