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ACYL REARRANGEMENT AND THE STRUCTURES OF SOME ESTERS RELATED TO PYRIDOXINE[1]

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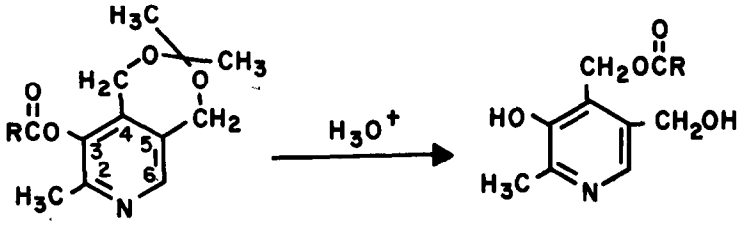
Acyl rearrangements are important in the chemistry of natural products, especially carbohydrates, steroids, and alkaloids. We wish to report a type of acyl rearrangement that occurs with pyridoxol and its derivatives, and to discuss its implications in the chemistry of vitamin B_6.

In an attempt to obtain 3-O-benzoylpyridoxol, we hydrolyzed 3-O-benzoyl-α^4, α^5-O-isopropylidenepyridoxol (I, R = Ph)[2] with dilute acid (hydrochloric or formic). The resulting monobenzoate gave a positive Gibbs (2,4-dichloroquinone-chlorimide) test, indicating an unsubstituted phenolic group, as would be expected from the rearranged product, such as II. Nevertheless, a rearrangement of the

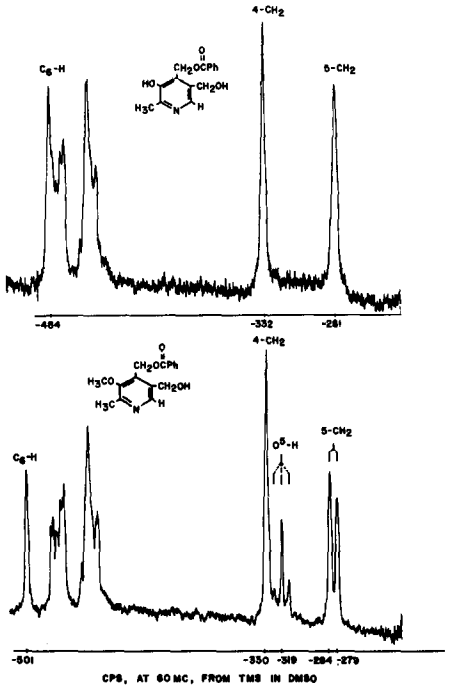


I II

expected 3-O-benzoylpyridoxol under the mildly alkaline conditions of testing could not be immediately ruled out, especially since acyl rearrangements are catalyzed by bases. The new benzoate was shown to be α^4-O-benzoylpyridoxol (II) as follows.

FIG. 1

A comparison of the NMR spectra of α^4-O-benzoylpyridoxol (top) and its 3-O-methyl ether (bottom)



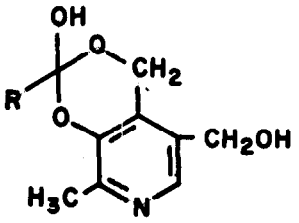
The NMR spectrum of the new benzoate (Fig. 1, top) was compared with that of its 3-O-methyl ether (Fig. 1, bottom), obtained by methylation with diazomethane in a mixture of tert. butanol and ether.[3] The NMR spectrum of the methylated product in DMSO shows the expected splitting pattern for an unsubstituted primary alcoholic group (triplet at -319 c.p.s.),[4] a two-proton doublet due to the splitting of the methylene protons by the hydroxylic proton, and a two-proton singlet for the methylene protons in the benzoylated hydroxymethyl group. In the parent benzoate, only the two

2-proton singlets of the methylene groups are evident, irrespective whether the hydroxymethyl groups are benzoylated or not.

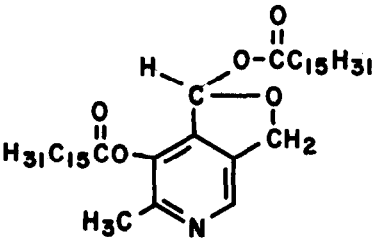
In the presence of an unsubstituted phenolic group, a fast exchange presumably takes place among the various positions that the alcoholic and phenolic protons can occupy, thus preventing these protons from giving rise to an NMR signal. Since this phenomenon has been observed in several other pyridoxol derivatives, it appears to be a reliable criterion for the presence of an unsubstituted phenolic group.[5] The new benzoate had the IR spectrum [$\nu_{\text{Max}}^{\text{Nujol}}$ 1704 (C = O), 3367 (alcoholic OH), 2688 (bonded OH), 717 cm.$^{-1}$ (benzoyl CH)] expected of structure II. Its m.p. (141-142°) and IR and NMR spectra were different from those of α^5-O-benzoylpyridoxol (m.p. 172-174°),[6] and accordingly its structure must be that of α^4-O-benzoylpyridoxol (II). This acid-catalyzed rearrangement of 3-O-acyl pyridoxol derivatives also occurs with the 3-O-p-nitrobenzoate (I, R = p-$PhNO_2$), 3-O-acetate (I, R = CH_3), and 3-O-palmitate (I, R = $C_{15}H_{31}$), and hence it provides a general method for the introduction of an acyl group into the 4-position of pyridoxol.

Having established the nature of the rearrangement, we turned our attention to some of its implications. Monoesterification of α^5-O-benzoylpyridoxol[6] with one mole of benzoyl chloride in pyridine gave α^4,α^5-O-dibenzoylpyridoxol, and not the expected 3-O,α^5-O-dibenzoylpyridoxol. If the 4-position was substituted, as in α^4-O-benzoylpyridoxol (II), the expected 3-O,α^4-O-dibenzoylpyridoxol was obtained. This indicates that the acyl rearrangement also takes place during acylation.

Most likely the rearrangement proceeds via the 3,4-orthoacid intermediate III, which is sterically favorable because of its six-membered orthoacid ring. Since a shift from α^4 to α^5 or vice versa has not been observed, it can be concluded that the formation of a cyclic orthoacid with a seven-membered ring including the α^4 and α^5 positions is less favorable, although a cyclic ketal with a seven-membered ring including these positions is formed quite readily.[2,6]



III



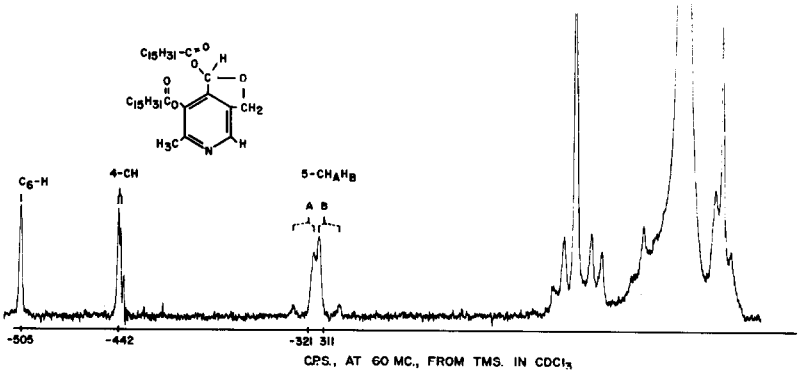
IV

Uchibayashi[8] has observed the formation of 3-O, α^4-O-diesters of pyridoxol in high yields on its partial esterification. The greater reactivity of the phenolic hydroxyl towards acylating agents has been demonstrated by us in selective benzoylation and mesylation experiments, but the apparently greater reactivity of the α^4 hydroxyl as compared with the α^5 hydroxyl is less obvious. Uchibayashi[8] attributed the reactivity of the α^4-hydroxy group to its para location with respect to the heterocyclic nitrogen. We believe that this effect is too small for the pronounced selectivity observed, and offer an alternative explanation based on the acyl rearrangement. Accordingly, monoesterification of the phenolic group is followed by an immediate rearrangement to the 4-position. Another monoesterification of the phenolic group does not lead to rearrangement, and thus 3-O, α^4-O-diesters are obtained.

The ease of the acyl rearrangement for pyridoxol led us to reinvestigate the reported[8] structure of 3-O, α^5-O-dipalmitoylpyridoxol, since we suspected that the compound would not be stable because of the likelihood of rearrangement. Palmitoylation of pyridoxal was the first step in the synthesis, and the product has been postulated[9] to have a 4-aldehyde structure. Nevertheless, the NMR spectrum of the product (Fig. 2) is consistent with the hemiacetal structure IV. The acetal proton is evident as a doublet ($J = 1.6$ c.p.s.), and the 5-methylene protons ($5\text{-}H_aH_b$) comprise an AB

FIG. 2

NMR spectrum of dipalmitoylpyridoxal



system. On irradiation of the methylene protons, the hemiacetal proton collapsed to a singlet, indicating that the hemiacetal proton is coupled with one of the methylene protons. The effect is probably transmitted either through the four single bonds (H-C-O-C-H), or through five bonds (H-C-C-C-C-H), the central one being part of the aromatic system. Reduction of the dipalmitoylpyridoxal IV with zinc, as described in the literature,[9] did not yield 3-O, α^5-O-dipalmitoylpyridoxol, but only the starting material. The data reported[9] (m.p., UV spectrum, and C and H analyses) for the presumed 3-O, α^5-O-dipalmitoylpyridoxol can be accounted for by the assumption that the compound is dipalmitoylpyridoxal (IV) and contains some impurities causing depression of the m.p. and a slight shift in the UV spectrum.

Other implications of this rearrangement, as well as its utility for synthesis through the selective esterification of the 4-position of pyridoxol, are being explored.

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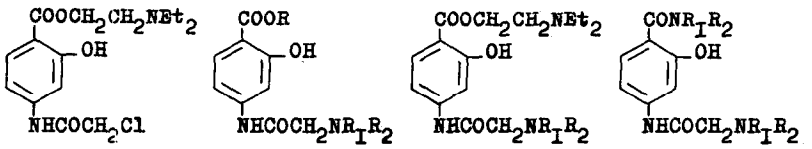
de Bender.

Par chauffage du chlorhydrate de I avec diverses amines, HNR_1R_2, dans un solvant polaire, éthanol ou méthanol, on obtient les dérivés II (R respectivement éthyle ou méthyle), résultant d'une réaction d'alcoolyse de l'ester, simultanée à la réaction de substitution de l'halogène de la fonction amide. L'alcoolyse peut être évitée en effectuant la réaction au sein d'un solvant non-polaire, tel que le benzène; on obtient alors les dérivés III. De même, par chauffage simple du chlorhydrate de I avec diverses amines sans solvant,



I II III IV

on obtient les dérivés III dans le cas d'amines de point d'ébullition bas, p.ex. diéthylamine et isopropylamine, tandis que dans le cas de la réaction avec une amine de point d'ébullition élevé, pipéridine, morpholine, benzylamine ou cyclohexylamine, on obtient les dérivés amidés IV, résultant d'une réaction d'aminolyse de l'ester diéthylaminoéthylique.

Les réactions d'alcoolyse et d'aminolyse du chlorhydrate de I sont bien en accord avec la théorie de la catalyse intramoléculaire. L'alcoolyse de l'ester diéthylaminoéthylique s'explique bien par le schéma de Bender, la présence de l'alcool comme solvant conduisant à des produits de solvolyse. Il est à remarquer que dans le cas de l'ester V, dans lequel la fonction phénolique se trouve être bloquée en tant qu'éther, nous n'avons pas constaté