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PHOTOALKYLATION OF NIKETAMIDE AND ITS ANALOGS

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Niketamide (I) and its isomeric analogs (II and III) were irradiated in methanol to afford a variety of photoalkylated products (IV∼XI), which reflected a pattern of orientation of the photoaddition.

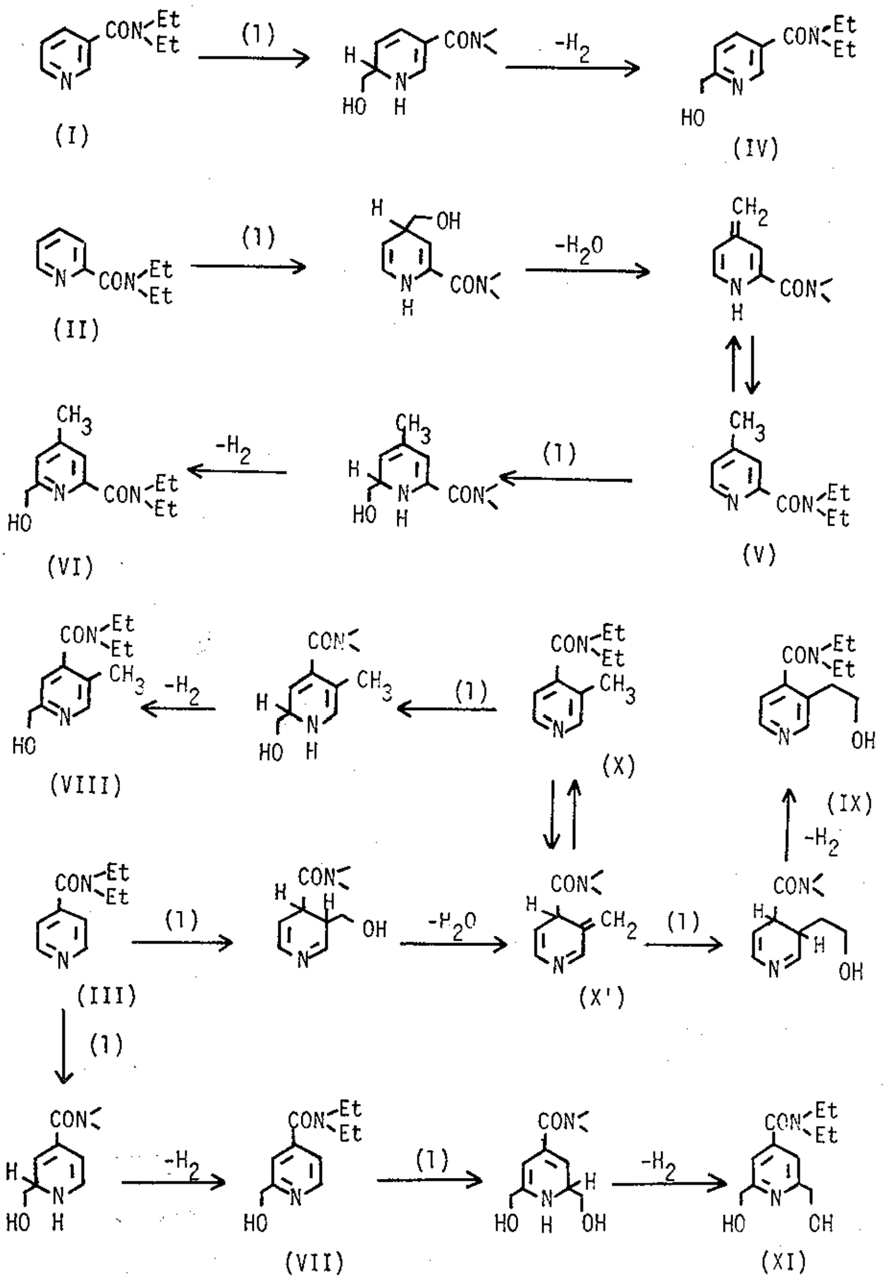
Although it has been reported that pyridine1) and a limited number of its analogs2),3) undergo photoaddition of CH_2OH and H radicals to the pyridine nucleus, no systematic study on the orientation of the addition has been done. We now wish to report the photochemistry of niketamide (I) and its isomeric analogs (II and III) in methanol, which demonstrated a pattern of orientation of radical addition to the pyridine nucleus.

Niketamide, N,N-diethylnicotinamide (I), as a 0.02 M methanolic solution, was irradiated with a low pressure mercury lamp at room temperature over a period of 37 hr. Upon chromatographic separation, a 6-methylol-introduced product (IV)(20 %)** was obtained. Irradiation of the hydrochloride of (I) did not give any isolable product.

On the other hand, irradiation of N,N-diethylpicolinamide (II) afforded many small peaks on g.l.c. and failed to give any products, whereas the hydrochloride of (II), after 66 hr irradiation, afforded two photoalkylated products, a 4-methyl derivative (V)(9.8 %) and a 4-methyl-6-hydroxymethyl derivative (VI)(15.4 %), which was also obtained by irradiation of the former (V) in 47 % yield. This suggested the reaction sequence of their formation.

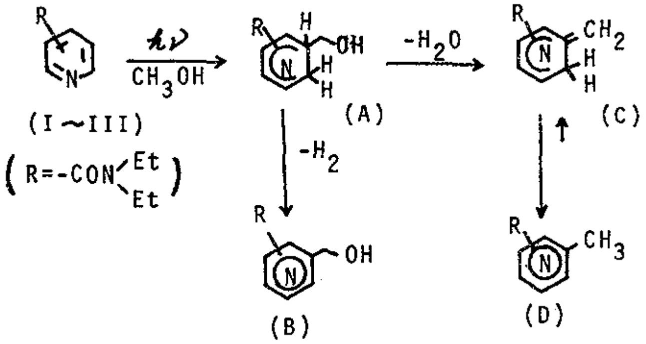
From the irradiation of N,N-diethylisonicotinamide (III) over a period of 21 hr, three photoproducts were isolated although in very small amounts : 2-hydroxymethyl (VII), 2-hydroxymethyl-5-methyl (VIII), and 3-(2-hydroxyethyl) (IX) derivatives. Furthermore, when 3-methyl-N,N-diethylisonicotinamide (X), which was not found in the reaction mixture upon irradiation of (III), was irradiated, two products (VIII and IX) were isolated. On the other hand, when the hydrochloride of (III) was employed, the photoproducts after 17 hr irradiation were 2-hydroxymethyl (VII)(18.2 %) and 2,6-bishydroxymethyl (XI)(11.3 %) derivatives. The structures of these photoalkylated products were established mainly by spectral evidence. The 3-(2-hydroxyethyl) derivative (IX) was readily converted by hydrolysis into the corresponding lactone (XII).

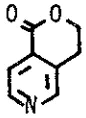
From these results, the course of the formation of these photoproducts is deduced as follows. Basically, these photoalkylations can be explained by the addition of radicals, formed according to the equation 1, to the pyridine nucleus.


CON<Et Et
(1)
-H2
HO
H
N
(I)
(IV)
(II)
CH2
-H2O
OH
CON<
CH3
(V)
(VI)
(VIII)
(X)
(IX)
(III)
(X')
(VII)
(XI)

The α-hydroxymethyldihydropyridine intermediate (A), though not isolated in these experiments, would undergo either dehydrogenation to the pyridylcarbinol (B) or dehydration to the methylpyridine (C⟷D).

$$\mathrm{CH_3OH} \xrightarrow{h\nu} \cdot\mathrm{CH_2OH} \quad + \quad \cdot\mathrm{H} \qquad (1)$$




(XII)

It is also deduced that a methylol group introduced at the 4-position of the pyridine nucleus is apt to undergo dehydration giving the exo-methylene intermediate (C) which would spontaneously isomerize to give the 4-methylpyridine derivative (D) as the final product, as in (V and VII). On the other hand, a methylol group introduced at the 2-position would be unaffected; therefore, dehydrogenation shows a greater tendency to give the pyridylcarbinol derivative (B), as in (IV, VI, VII, VIII, and XI).

The formation of the 3-(2-hydroxyethyl) derivative (IX) would be explained by the addition of a methylol radical to the exo-methylene intermediate (X'),4) a tautomeric form of (X), followed by dehydrogenation.

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** Figures in parenthese show yield percentages.

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