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A NOVEL APPROACH TO CYCLIC β-CARBONYL-ENAMINES $\Delta^{7,8}$-LYSERGIC ACID DERIVATIVES VIA THE POLONOVSKI REACTION.

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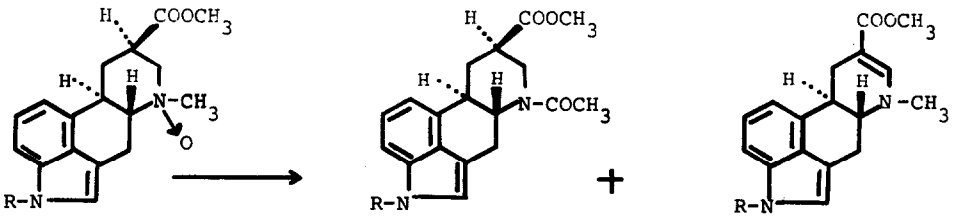
Cyclic vinylogous amides, e.g. 1,4,5,6-tetrahydronicotinic acid derivatives have repeatedly been demonstrated to be useful intermediates in organic synthesis [1]. So far, the latter are accessible only by partial hydrogenation of the corresponding N-quarternary nicotinic acid derivatives [1].

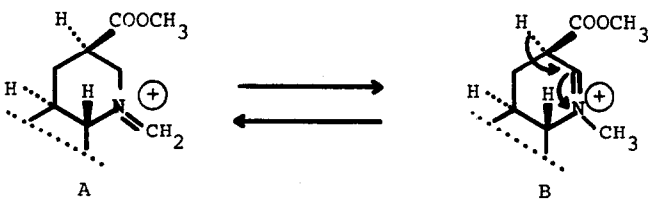
In connection with our synthesis of 6-nor-lysergic acid [2], we investigated the reaction of the N-oxide 1 (R=H) m.p. 193-195° (dec.) with acetic anhydride in chloroform. When the reaction was complete, two main products were separated by silicagel chromatography. The more polar one, m.p. 290° (dec.) $[\alpha]_D^{20} = -210°$ (c=1, DMSO), isolated in about 10% yield, was identical with the authentic 6-nor-6-acetyl-derivative 2 (R=H) prepared by acetylation of 6-nor-9,10-dihydrolysergic acid methylester [2]. It is thus the product expected from a normal Polonovski reaction.



1 2 3

The less polar product m.p. 232-234° (dec.) $[\alpha]_D^{20} = -254°$ (pyridine) could be obtained in 24% yield and has been assigned structure 3 (R=H) on the basis of its stability to alkaline hydrolysis [3] and the following spectroscopic evidence: $C_{17}H_{18}N_2O_2$ (282.3): $M^+ = 282$, λ_{max} (CH_2Cl_2) 223 nm (log ε 4.50) 292 nm (log ε 4.39), $\tilde{\nu}$(CH_2Cl_2) 1610, 1625, 1680 cm^{-1}, nmr ($CDCl_3$) 3.05(s,3H) 3.75(s,3H) 7.4(s,1H) ppm. These data are characteristic of N-methyl-1,4,5,6-tetrahydronicotinic acid methylester [3].

Since 2 is probably formed [4] after hydrolysis of the intermediate immonium salt A, and 3 by deprotonation of B, we reasoned that an existing tautomeric equilibrium between A and B could be shifted by transforming B into the stabilised enamine 3 with a relatively strong base e.g. triethylamine TEA or 1,4-diazabicyclo[2,2,2]octane.

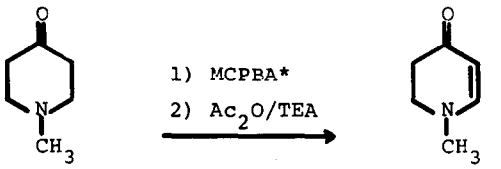


A B

Indeed, 3 (R=H) could be conveniently prepared in a one-pot reaction from 9,10-dihydrolysergic acid methylester in 45-50 % yield by the general reaction as given below for the preparation of 5. Less than 3 % of compound 2 (R=H) was formed! Similarly, 3 ($R=CH_3$) m.p. 179-180° $[\alpha]_D^{20} = -220°$ (pyridine) was isolated in 47 % yield and only traces of 2 ($R=CH_3$) were detected. The modest yields seem to be due only to decomposition during isolation. Acetic anhy-

dride could be replaced by propionic- or benzoic anhydride without affecting the yield but with pyridine as base poorer results were obtained.

The usefulness of this reaction is demonstrated by the preparation of the pyridinone 5 in 50 % yield from N-methylpiperidone-4 4. Compound 5 has been described recently [5] and was obtained in 3 steps by the method of Winterfeldt [6] starting from the relatively unaccessible 4-methoxy-pyridine.



4 5

After completion of our work, another application of the Polonovski reaction has been published [8]. Starting from N-methylpiperidine-N-oxide, 3-trifluoroacetyl-N-methyl-piperideine-2 was obtained. This very specific reaction, however, could not be generalised under our reaction conditions and led only to complex mixtures.

The following synthesis of 5 is typical: Into a stirred solution of 1.18 ml (10 m moles) of freshly distilled N-methyl-piperidone-4 in 20 ml of abs. CH_2Cl_2 is added at -40°C a solution of 11 equiv. of MCPBA* in 20 ml of CH_2Cl_2. After stirring at this temperature for 30 minutes 1.04 ml (11 m moles) of acetic anhydride and 6.9 ml (50 m moles) of triethylamine are added to the clear solution which is then stirred for additional 60 minutes at 0°. Work up with ice-cold $NaHCO_3/CH_2Cl_2$ affords an oil which distils at 110°/1 mm Hg to yield 0.55 g (ca.50%) of 5 as a yellowish oil. nmr ($CDCl_3$): 2.5(t,2H,J=8) 3.1(s,3H) 3.5(t,2H,J=8) 4.85(d,1H,J=8) 7.1(d,1H,J=8) [5].

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*) MCPBA = m-chloroperbenzoic acid

Thus, the Polonovski reaction, which has already been shown to yield cyclic enamines in the case of nupharidine [7], appears to be also applicable for the synthesis of vinylogous amides in a modified form.

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