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REACTION OF N-(4-PYRIDYLMETHYL)-AMIDE N-OXIDES WITH ACETIC ANHYDRIDE

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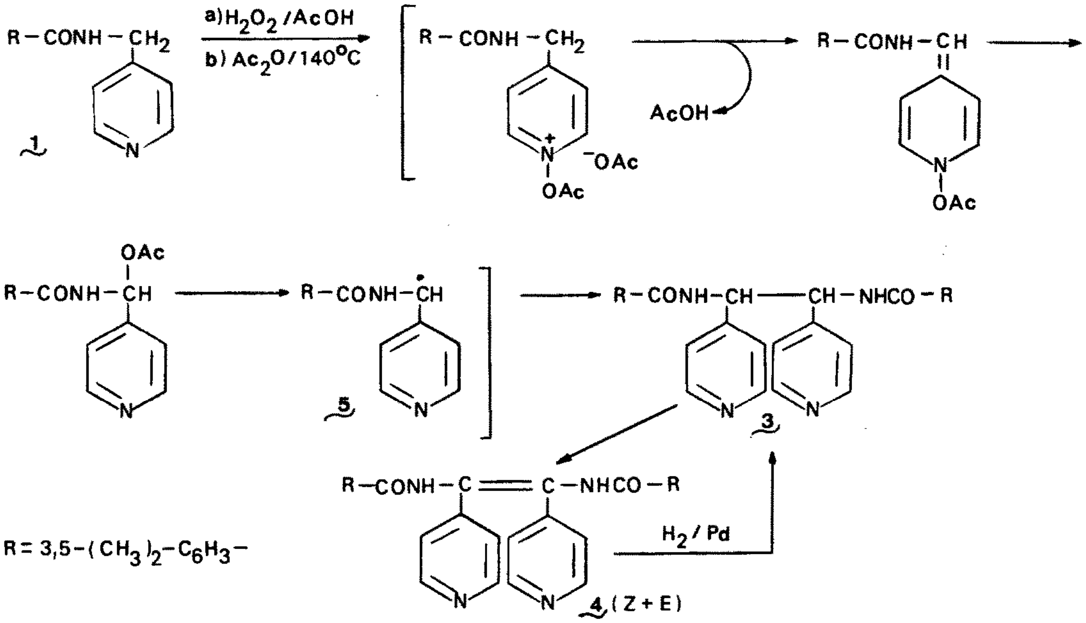
Summary: Reaction of N-(4-pyridylmethyl)-benzamide N-oxides with acetic anhydride yielded dimerization compounds. This dimerization occurs at the atom attached to the pyridine ring.

N-(4-pyridylmethyl)-3,5-dimethylbenzamide[1] **1** is a powerful neuroleptic agent, its N-oxide[2] **2** being the main metabolite. The search for new derivatives of **1** as well as the theoretical interest of the reaction of heteroaromatic N-oxides with acetic anhydride which has been excellently reviewed by Oae and Ogino[3] prompted us to study the reaction of **2** with this reagent, which resulted in a new type of dimer not previously reported.

When **2** was treated with acetic anhydride under reflux for 1.5 hours a white solid (42%) appeared. This compound was recrystallized from DMF, m.p. 336-8°C to give a compund identified as N,N'-di-(3,5-dimethylbenzoyl)-1,2-di-(4-pyridyl)-ethylenediamine **3**, according to its spectroscopic data. MS : 478 (M^+), 240 (M^+)/2 + 1); IR (KBr) : 3300 and 1630 (NH and CO amide); ^{1}H-NMR (F_3C-COOH 90 MHz): 2.30 (s, 12H, $4CH_3$), 6.80 (s, 2H, 2CH), 7.20 (s, 4H, 4H ortho-phenyl), 7.35 (s, 2H, 2H para-phenyl), 8.60 (d, 4H, 4H β-pyridine), 8.90 (d, 4H, 4H α-pyridine). Removal, under reduced pressure of the mother liquors produced a solid (22%), m.p. 280-2°C (DMF-water) which showed absorption bands in IR near 3200 and 1650 cm^{-1} due to the amide NH and CO respectively. The mass spectrum showed a molecular peak at 476 which suggested a structure similar to **3** in which the loss of two hydrogen atoms has taken place. The fact that signals due to the methine protons had disappeared in the NMR spectrum suggested that the compound could be a mixture of the Z and E isomers of N,N'-di-(3,5-dimethylbenzoyl)-1,2-di-(4-pyridyl)-vinylenediamine **4**. ^{1}H-NMR spectrum ($CDCl_3$ 90 MHz) : 2.39 (s, 12H, $4CH_3$), 7.18 and 7.45 (two doublets corresponding to the 4 hydrogen atoms of the β position of the pyridine ring in the Z/E mixture), 7.28 (s, 2H, 2H para-phenyl), 7.55 (s, 2H, 2H ortho-phenyl), 7.63 (s, 2H, 2H ortho-phenyl), 8.46 and 8.59 (two doublets corresponding to the 4 hydrogen atoms of the α position of the pyridine ring in the Z/E mixture).

Catalytic hydrogenation of **4** yielded **3** which confirmed the structural relationship between the compounds.



The fact that 3 and 4 were isolated seems to suggest that the reaction takes place via a homolytic cleavage process giving rise to radicals 5, dimerization of which explains the formation of 3. The latter, in a transfer reaction followed by a radical disproportionation process would give rise to 4. The presence of radical precusors or inhibitors does not seem to modify the yield of either 3 or 4 suggesting that the reaction follows a "radical cage" mechanism similar to that observed by Oae and Traynelis[4] for other N-oxides.

In order to comfirm the extension of this dimerization reaction other N-(4-pyridylmethyl)-amide N-oxides were treated with acetic anhydride under the same conditions to give the corresponding N,N'-diacyl-1,2-di-(4-pyridyl)-ethylendiamines with R alkyl or aryl groups.

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