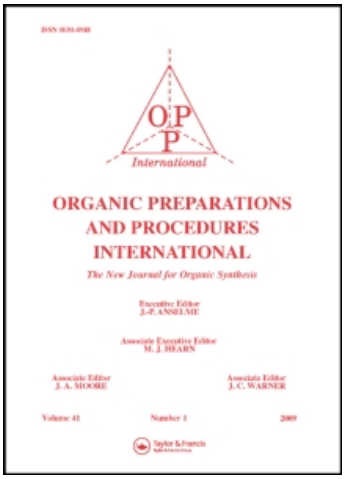

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FORMATION OF A NEW TYPE OF 1:2 ADDUCT FROM THE REACTION OF 2,3-LUTIDINE N-OXIDE WITH PHENYL ISOCYANATE

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OPPI BRIEFS

FORMATION OF A NEW TYPE OF 1:2 ADDUCT FROM THE REACTION OF 2,3-LUTIDINE N-OXIDE WITH PHENYL ISOCYANATE

Submitted by (12/22/78) T. Hisano, M. Ichikawa, T. Matsuoka, K. Muraoka† and M. Hamana††

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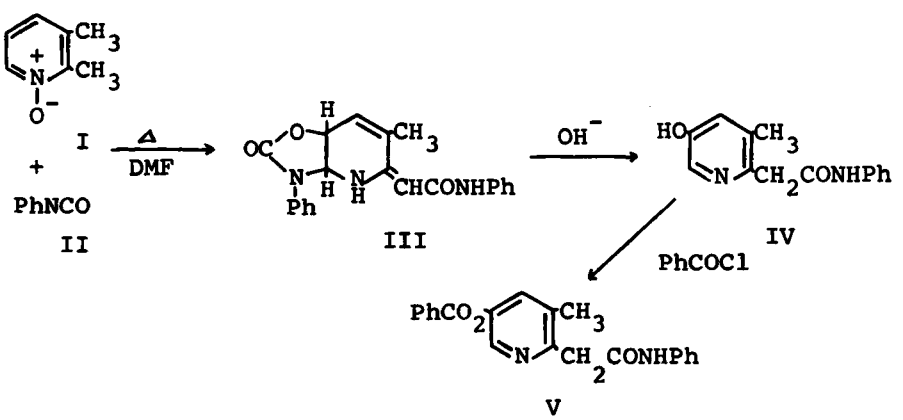
As an extension of the study on the 1,3-dipolar cycloaddition of pyridine N-oxides,[1] we carried out the reaction of 2,3-lutidine N-oxide (I) with phenyl isocyanate (II) and obtained a new type of 1:2 adduct (III) of I and II as colorless prisms, mp. 227-229° in 21% yield.

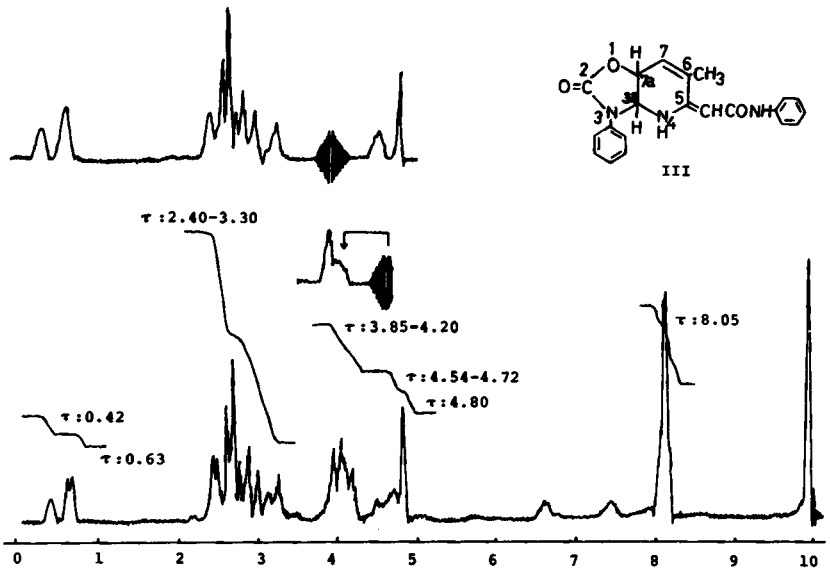


The analytical values of III were in agreement with the empirical formula $C_{21}H_{19}O_3N_3$, and its mass spectrum indicated that III is a 1:2 adduct of I and II. The infrared (IR)

spectrum (see Experimental) was characteristic of 2-oxo-oxazolo[4,5-b]pyridines formed from pyridine N-oxides and II.[1,2] The nmr spectrum was consistent with the assignment. The proton at the 4-position (doublet at τ 0.63) and the proton of the amide of the side-chain (broad singlet at τ 0.42) disappeared upon the addition of D_2O. Spin decoupling experiments further confirmed these assignment (Fig. 1).

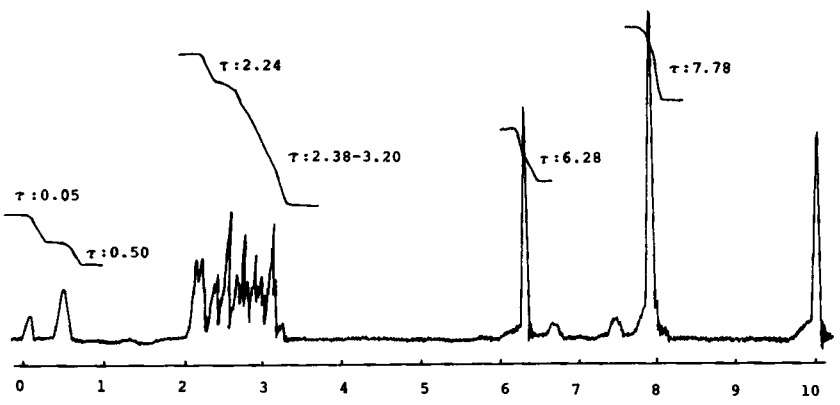
On the basis of these observations, we assigned 2,3,4,5,3a,7a-hexahydro-2-oxo-3-phenyl-5-(N-phenylcarbamoyl)-methylene-6-methyl-oxazolo[4,5-b]pyridine to product (III). The use of one equivalent II in the above reaction caused the decrease of the yield of III to 12%, and attempts to obtain a 1:1 adduct by changing I/II ratios was not successful yet.

Upon refluxing in ethanolic potassium hydroxide, III readily lost a component of II and was converted to 2-N-phenylcarbamoylmethyl-3-methyl-5-pyridinol (IV) as colorless needles, mp. 245-246°, in a high yield of 95%. The structure of IV was confirmed by the elemental analysis [$C_{14}H_{14}O_2N_2$], the mass spectrum [M^+: m/e 242] and the appearance of a broad band due to a hydroxyl group at 2200-3400 cm^{-1} similar to that of 3-pyridinol[3] and the absence of the carbonyl band at 1715 cm^{-1} observed in the IR spectrum of III. The nmr spectrum of IV is full agreement with the proposed structure (Fig. 2). Treatment of IV with benzoyl chloride and triethylamine in boiling acetone afforded the corresponding O-benzoate (V) as colorless needles, mp. 140-142°, in 77% yield; conversely V was easily hydrolyzed by hot 10% sodium hydroxide solution to IV.



III

Fig. 1. NMR Spectrum of Compound III (in d_6-DMSO at 100 Mc)



IV

Fig. 2. NMR Spectrum of Compound IV (in d_6-DMSO at 100 Mc)

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded on Nippon Bunko DS-301 infrared spectrophotometer equipped with grating. ^{1}H-NMR spectra were taken with JNM-MH-100 and JNM-C-60-H spectrometers in ca 5%(w/v) solution with tetramethylsilane as an internal standard and chemical shifts are expressed in τ values. MS spectra were taken with JEOL-JMS-01SG spectrometer.

Reaction of 2,3-Lutidine N-oxide (I) with Phenyl Isocyanate (II).- To a solution of 2.50 g (0.02 mole) of I in 16.4 ml of DMF was added dropwise 4.85 g (0.04 mole) of II with stirring at room temperature and the reactants were heated at 110° for 7 hrs. The reaction mixture was concentrated in vacuo and then 20 ml of ether was added to the residue. After standing overnight at 0-5°, the precipitated crystals were collected and recrystallized from acetone to give 2,3,4,5,3a,7a-hexahydro-2-oxo-3-phenyl-5-(N-phenylcarbamoyl)methylene-6-methyloxazolo[4,5-b]pyridine (III) as colorless prisms, mp. 227-229°, in 21% yield.

IR ν_{max}^{KBr} cm^{-1}: 3300 (-NH-), 1715 and 1660 (C=O). NMR (d_6-DMSO) at 100 MHz: τ 8.05 (3H, narrow d, CH_3), 4.80 (1H, s, =CH-), 4.54-4.72 (1H, m, C_{7a}-H), 3.85-4.20 (2H, m, C_7- and C_{3a}-H), 2.40-3.30 (10H, m, two phenyl C-H), 0.63 (1H, d, J_{4-3a} = 3 Hz, 4-H), 0.42 (1H, broad s, -CONH-). Mass spectrum: M^+ m/e: 361, 317 (M^+-CO_2), 269 (M^+-NHPh), 242 (M^+-CONH-Ph).

Anal. Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63.
Found : C, 69.81; H, 5.38; N, 11.98.

Hydrolysis of III.- A mixture of 1.0 g of III and 10 ml of 2.5% EtOH-KOH was refluxed for 1 hr. The solvent was removed

in vacuo and then 10 ml of H_2O was added to the residue. The alkaline solution was neutralized with 10% HCl. The precipitated crystals were collected and recrystallized from acetone to give IV as colorless needles, mp. 245-246°, in 95% yield. IR ν_{max}^{KBr} cm^{-1}:3225 (-NH-), 2200-3400 (-OH), 1655 (C=O). NMR (d_6-DMSO) at 100 MHz: τ 7.78 (3H, s, CH_3), 6.28 (2H, s, $-CH_2-$) 2.38-3.20 (6H, m, phenyl, C_4-H), 2.24 (1H, d, J_{6-4} = 2.6 Hz, C_6-H), 0.50 (1H, broad s, -CONH-), 0.05 (1H, broad s, OH).[4] Mass spectrum: M^+ m/e: 242.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.46; H, 5.83; N, 11.56.
Found : C, 69.54; H, 5.72; N, 11.59.

Reaction of IV with Benzoyl chloride.- To a solution of 500 mg (0.002 mole) of IV and 5 ml of Et_3N in 70 ml of acetone, 320 mg (0.0025 mole) of benzoyl chloride was added dropwise and the mixture was refluxed for 1 hr. After cooling, triethylamine hydrochloride precipitated and was filtered. The filtrate was evaporated in vacuo and triturated with 30 ml of ether to give a crystalline mass, which was filtered, washed with H_2O and recrystallized from acetone, giving 550 mg (77%) of colorless needles of V, mp. 140-142°.

IR ν_{max}^{KBr} cm^{-1}: 3300 (-NH-), 1720 and 1645 (C=O). NMR ($CDCl_3$) at 60 MHz: τ 7.58 (3H, s, CH_3), 6.12 (2H, s, $-CH_2-$), 1.74-3.05 (11H, m, pyridine C_4- and two phenyl C-H), 1.66 (1H, d, J_{6-4} = 2.6 Hz, pyridine C_6-H), 0.67 (1H, broad s, -CONH-). Mass spectrum: M^+ m/e: 346.

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09.
Found : C, 72.82; H, 5.12; N, 8.03.

Hydrolysis of V with hot 10% NaOH aq. soln. for a short period of time gave IV in good yield.

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3. C. J. Pouchert, "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Inc., 1970, p. 967.
4. A 5% solution of an authentic sample of β-hydroxypyridine in d_6-DMSO was used for assigned identification.

TETRACHLOROCYCLOPROPENE, A HIGHLY REACTIVE REAGENT FOR 4(1H)-PYRIDINONE SYNTHESIS

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The 1,3-dipolar cycloaddition of cyclopropenes and cyclopropenones with various mesoionic five-membered heterocycles affords 1,4-dihydropyridines and 4(1H)-pyridinones with substitution patterns which are fixed by the choice of reactants.[1] Substituents at C_3, C_4 and C_5 of the pyridinyl product derive