

A Novel Synthesis of Pyridine *N*-Oxides and Isoxazolines

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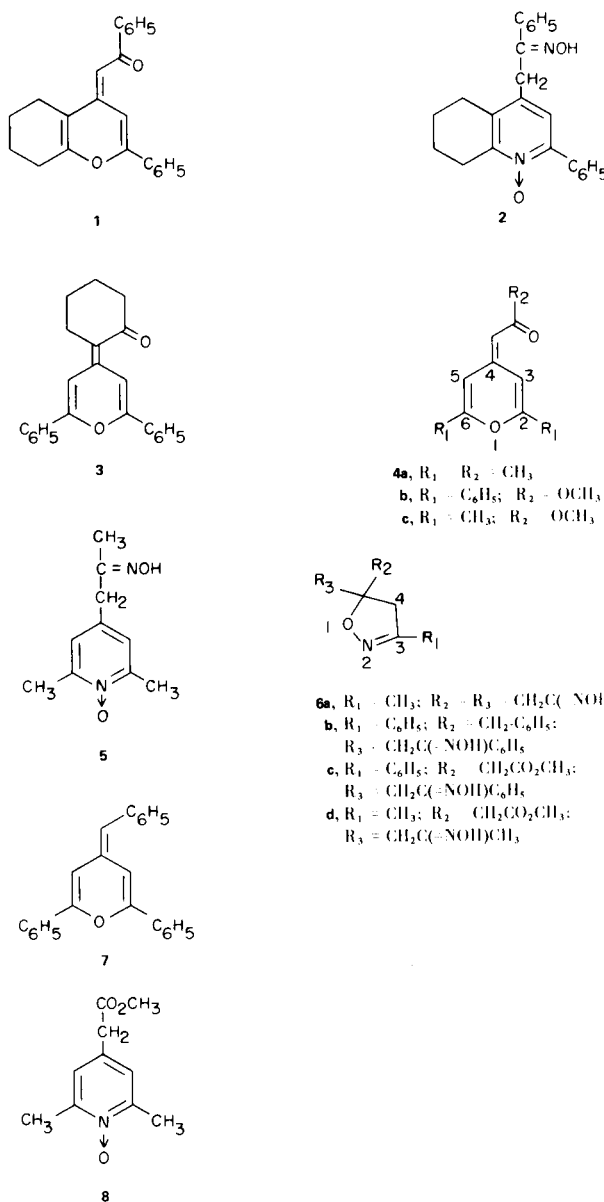
Sir:

We wish to report that the reaction of ketonylidene-pyrans with hydroxylamine constitutes a satisfactory route to pyridine *N*-oxides and sometimes to non-readily available isoxazolines.

Treatment of the phenylmethylenepyran (1) (2) with hydroxylamine hydrochloride in refluxing ethanol-pyridine solution affords, in 85% yield, the substituted pyridine *N*-oxide (2) m.p. 234-235°, exhibiting a characteristic ultraviolet absorption (3) at  $\lambda$  max 215 nm ( $\log \epsilon$  4.29) and 246 nm ( $\log \epsilon$  4.52), nmr signals (DMSO) at  $\delta$  4.06 ( $-\text{CH}_2\text{-C}=\text{NOH}$ ), 6.92 (C-3H), and a one proton chemical shift at 11.50 ppm (N-OH), readily exchanged with deuteriowater, as well as a mass spectrum fragmentation pattern at  $m/e$  358 ( $\text{M}^+$ ), 342 ( $\text{M}^+-16$ ), typical of *N*-oxides (3,4). The same compound (2) is formed (in 82% yield) when the cyclohexanone-2',6'-diphenylpyranlydene (3) (2) is allowed to react with hydroxylamine under identical experimental conditions. Formally, in both cases, this implies the opening of the pyran ring and formation of a  $\delta$ -diketone which then recycles.

Since chromones are known to afford isoxazoles by reaction with hydroxylamine (5), one could anticipate that sometimes the formation of pyridine *N*-oxide would compete with that of isoxazoline. Indeed, reaction of 4-acetonylidene-2,6-dimethylpyran (4a) (6) with hydroxylamine furnishes a 6:1 mixture of the substituted *N*-oxide derivative (5) (78%) and the isoxazoline (6a) (13%). Compound 5, m.p. 159-161°, [ $\lambda$  max 216 nm ( $\log \epsilon$  4.47), 262 nm ( $\log \epsilon$  4.17),  $m/e$  194 ( $\text{M}^+$ ), 178 ( $\text{M}^+-16$ )], shows typical nmr signals ( $d_5$ -py) at 1.9 (Me), 3.45 ( $-\text{CH}_2\text{-C}=\text{NOH}$ ), and 7.0 ppm (C-3H, C-5H). Both methyl signals at C-2 and C-6 appear as a singlet at 2.46 ppm thus supporting the symmetrical pyridine *N*-oxide structure (5). The isoxazoline (6a) m.p. 154-155°, [ $m/e$  227 ( $\text{M}^+$ )], does not display any ultraviolet absorption above 220 nm, but exhibits characteristic nmr signals ( $d_5$ -py) at 1.75 (C-3 Me), 2.18 (2 x  $\text{CH}_3\text{-C}=\text{NOH}$ ), 2.75 (2 x  $\text{CH}_2\text{-C}=\text{NOH}$ ), and a two proton signal at 12.4 ppm (N-OH, exchanged with deuterium oxide). Hence, it appears that hydroxylamine causes cleavage of the carbon-oxygen bond of the ketonylidene-pyran (4a). Heterocyclic cyclization then occurs either at position 6 followed by

elimination of water providing the substituted pyridine *N*-oxide (5), or at C-4 affording the isoxazoline (6a).



A carbonyl group conjugated with the methylenepyran seems to be a requisite for the formation of pyridine *N*-oxide under these conditions, because reaction of 4-benzylidene-2,6-diphenylpyran (**7**) with hydroxylamine only yields the isoxazoline (**6b**), m.p. 159-161°, [ $\lambda$  max 258 nm (log  $\epsilon$  4.16), m/e 370 ( $M^+$ )] in 73%. The nature of the carbonyl group does not seem to be crucial, since both ketones and esters can lead to pyridine *N*-oxides. Indeed, whereas the ester (**4b**) (**8**) affords exclusively the isoxazoline (**6c**), m.p. 108-110°, [ $\lambda$  max 211 nm (log  $\epsilon$  4.28), 2.58 nm (log  $\epsilon$  4.23), nmr (deuteriochloroform) 2.86 (C-4CH<sub>2</sub>), 3.62 (CO<sub>2</sub>Me), m/e 325 ( $M^+$ )] in 98% yield, the ester (**4c**) provides a 2:3 mixture of pyridine *N*-oxide (**8**) m.p. 106-108°, [ $\lambda$  max 216 nm (log  $\epsilon$  4.42), 262 nm (log  $\epsilon$  4.17), nmr (deuteriochloroform) 2.52 (2 x Me), 3.73 (CO<sub>2</sub>Me), 7.13 ppm (C-3H, C-5H), ms m/e 195 ( $M^+$ ) 179 ( $M^+-16$ )], and isoxazoline (**6d**), [nmr (deuteriochloroform) 1.93 (2 x Me), 3.64 (CO<sub>2</sub>Me), 7.9 ppm (NOH), ms m/e 228 ( $M^+$ )].

The various factors responsible for the competitive formation of pyridine *N*-oxides and isoxazolines from methylenepyran will be discussed in detail in the forthcoming full paper.

Satisfactory spectral data and elemental analyses within  $\pm 0.3\%$  of calculated values were obtained for all compound described.

#### REFERENCES

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