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C-NITROSATION OF UNSATURATED AMIDES. A ROUTE TO 2-PYRONE IMINES

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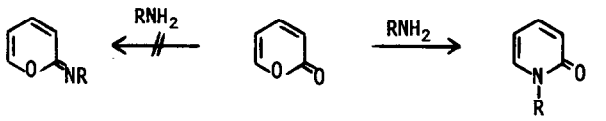
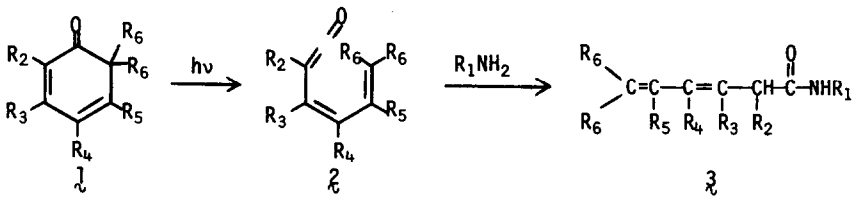
It is well known[1] that 2-pyrones usually react with primary amines to give 2-pyridones, not 2-pyrone imines. We have discovered, by chance, a route to 2-pyrone imines. The reaction



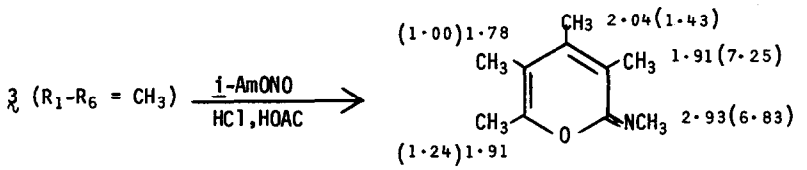
is not only synthetically useful but mechanistically interesting; it involves preferential C- rather than N-nitrosation of an unsaturated amide, and was discovered in the following way.

Irradiation of 2,4-cyclohexadienones (1) in the presence of amines constitutes a general, high yield synthesis of unsaturated amides of the type 3, through nucleophilic capture of the intermediate ketenes 2.[2] However, with highly substituted dienones (for example, R_2-R_6 = CH_3)



the intermediate ketene cannot be trapped by weak nucleophiles such as water or methanol.[3] Consequently the unsaturated acids or esters become accessible by this route only from the corresponding amides. However these hindered amides strongly resist acidic or alkaline solvolysis. Nitrosation, which has been used to convert hindered amides to acids,[4] can provide a way around this difficulty.

Irradiation of 1 (R_2-R_6 = CH_3) in ether saturated with methylamine gave 3 (R_1-R_6 = CH_3), mp 74.8-75.2° in 89% yield.[5,6] Nitrosation[7] of 3 (R_1-R_6 = CH_3) gave as the major product (67%) a crystalline compound,[6] mp 57-58.5°, to which we assign the 2-pyrone imine structure 4. The nmr spectrum[8,9] was consistent with structure 4 or possibly with that of the isomeric



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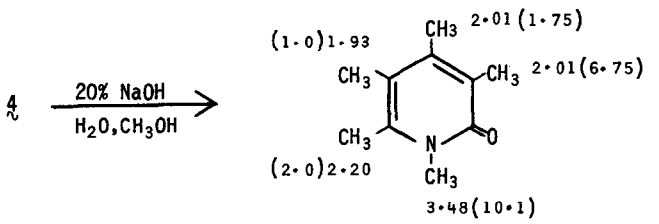
N-methylpyridone structure 5; the ir and uv spectra also did not permit a clear-cut distinction between these two possibilities. However the mass spectrum[10] clearly favored structure 4. In particular, it showed a base peak at M-41 ($CH_3N{\equiv}C$) and no significant peak at M-28 (CO); it is well known that 2-pyridones[11] and 2-pyrones[12] generally show a prominent peak for loss of carbon monoxide,[13] and it is reasonable that 2-pyrone imines would show a corresponding loss of RNC.[14]

This reasoning was confirmed when we were able to synthesize 5 through treatment of 4 with 20% aqueous sodium hydroxide in methanol (5:3) at 160-180° for 4 hr. Compound 5,



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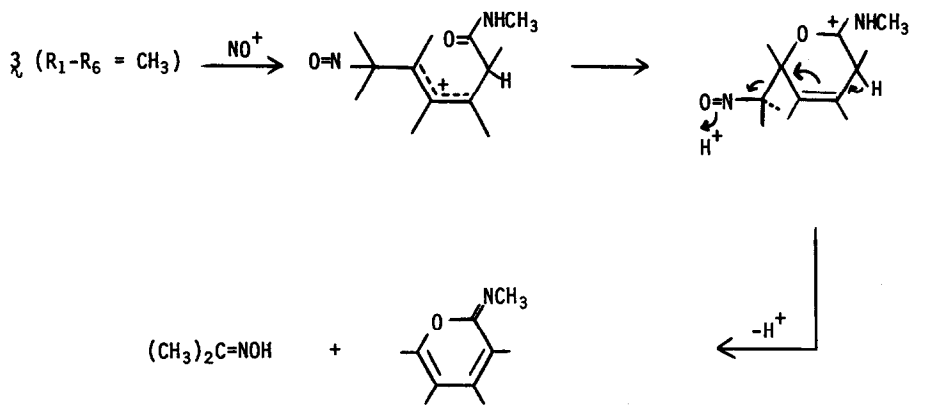
mp 99-100°, was obtained in 74% yield. The mass spectrum of 5 showed an important M-CO peak.[15,16]

A mechanism for the formation of 4 from 3 is shown:



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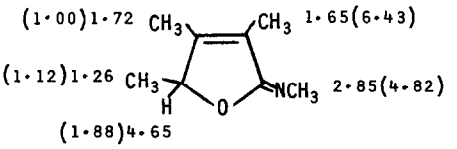
Nitrosation occurs on carbon rather than on nitrogen, and the 3-carbon fragment is lost as acetone oxime. Indeed, we were able to isolate small amounts (<6%) of acetone oxime from the product mixture, although control experiments showed that the oxime is largely destroyed under the nitrosation reaction conditions.

A second product, minor and very labile, was isolated (8%) from the nitrosation of 3 (R_1-R_6 = CH_3).[17] We tentatively assign it the imino butenolide structure 6. In particular, its nmr spectrum has the methine proton at lower field and the C-4 methyl at higher field than



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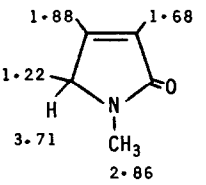

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the known[18] pyrrolinone isomer 7; the mass spectrum of 6 (and of its N-cyclohexyl analog) also favors a structure having the oxygen in the ring.[19]

We believe that 2-pyrone imines are a novel or rare class of compounds, highly substituted derivatives of which become readily accessible through the route described here.

Acknowledgement. We are indebted to the National Institutes of Health (GM 15997) for financial support of this research.

References and Notes

1. For a review, see N.P. Shusherina, N.D. Dmitrieva, E.A. Luk'yanets and R.Ya. Levina, Russian Chem. Rev., 36, 175 (1967).
2. D.H.R. Barton and G. Quinkert, J. Chem. Soc., 1 (1960); for reviews, see G. Quinkert, Angew. Chem., Intern. Ed. Engl., 4, 211 (1965) and 12, 1072 (1972).
3. H. Hart, P.M. Collins and A.J. Waring, J. Am. Chem. Soc., 88, 1005 (1966), J. Griffiths and H. Hart, ibid., 90, 3297 (1968).
4. N. Sperber, D. Papa and E. Schwenk, ibid., 70, 3091 (1948); G. Pala, T. Bruzzese, E.M. Uberti and G. Coppi, J. Med. Chem., 9, 603 (1966).
5. 22.5 g of 1 (R_2-R_6 = CH_3) in 500 ml of ether through which methylamine has been bubbled at room temperature for 45 min, 450 W Hanovia lamp, Pyrex filter, 3.5 hr.
6. All new compounds gave satisfactory elemental analyses and spectra (ir, nmr, uv, mass) consistent with the assigned structures.
7. In a typical experiment, 11.0 g of 3 (R_1-R_6 = CH_3) in 200 ml of glacial acetic acid was flushed with nitrogen and saturated with hydrogen chloride. Isoamyl nitrite (21.2 ml) was added dropwise (2 hr) and the mixture was heated at 100° for 4.5 hr. The cooled mixture was diluted with water containing a little hydrochloric acid (pH 1) and extracted with ether to remove neutral and acidic products. The pH was raised to 12; ether extraction and workup gave 4, which was recrystallized from pentane at -78°.
8. Chemical shifts, shown on the structure, are in ppm (δ) from internal TMS; relative slopes of downfield shifts with added $Eu(fod)_3$ are shown in parentheses; see D.R. Kelsey, J. Am. Chem. Soc., 94, 1764 (1972).
9. Treatment with MeONa/MeOD for one week at room temperature resulted in disappearance of the signals at δ1.91 and 2.04.
10. m/e (relative intensity), 70eV: 165(24), 124(100), 109(59), 81(18).
11. For examples, see R. Lawrence and E.S. Waight, J. Chem. Soc., B, 1 (1968).
12. For leading references, see H. Budzikiewicz, C. Djerassi and D.H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, Inc., San Francisco, 1967, p. 208.
13. For a general discussion see G. Spiteller in "Physical Methods in Heterocyclic Chemistry", ed. by A.R. Katritzky, Academic Press, Inc., New York, 1971, Vol. 3, p. 223.
14. We have prepared analogs of 4 with the N-methyl replaced by cyclohexyl and benzyl; all show (M-RNC) as the base peak in their mass spectra.
15. m/e (relative intensity), 70eV: 165(100), 137(30), 136(77), 122(41), 56(25).
16. Compound 5 was also synthesized by methylation of tetramethyl-2-pyridone (some 2-methoxy tetramethylpyridine was also formed), which in turn was prepared by hydrogenolysis of N-benzyl-tetramethyl-2-pyridone (glac. HOAc, Pd/C) which was prepared from 3 (R_1 = benzyl, R_2-R_6 = CH_3) via routes analogous to the preparation of 4 and 5.
17. The same type of product was obtained in 26% yield from 3 (R_1 = cyclohexyl, R_2-R_6 = CH_3).
18. D. Seebach, Chem. Ber., 96, 2723 (1963).
19. There is an intense peak at M-43 (CH_3CO) in the spectra of the N-methyl and N-cyclohexyl compounds. This is entirely analogous to the mass spectrum of α-angelicalactone (4-hydroxy-2-pentenoic acid lactone); "Atlas of Mass Spectral Data", Ed. by E. Stenhagen, S. Abrahamsson and F.W. McLafferty, Interscience Publishers, Inc., New York, 1969, Vol. I, p. 219.