Addition of Picolyl Anions to α,β-Unsaturated Carbonyl Derivatives (1)

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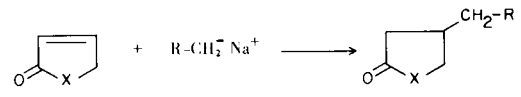
As part of a study designed to clarify the structural and conformational requirements for cholinergic activity of pilocarpine through the synthesis of derivatives of type **3**, the Michael condensation of 2- and 4-picolyl anions to 2(5*H*)furanone and 2-cyclopentenone was investigated. Michael additions to Δ^1-butenolides have received relatively little attention. The successful addition of an active methylene to 2(5*H*)furanone was reported by Preobrazhenskii and co-workers (3) and 1,4-addition of thiols and amines to 4-hydroxy-2-pentenioc acid lactone has been demonstrated (4). The additions of the anions derived from 2- and 4-picoline to 2- and 4-vinyl pyridine are well known (5). However, the addition of the 2-picolyl anion to benzalacetophenone yields only dimeric and trimeric products (6). The Michael addition of anions derived from "activated" picolines proceeds more normally. Thus, the anions derived from 2-pyridylacetonitrile and 2-pyridylacetone are reported to add smoothly to α,β-unsaturated ketones and nitriles (7). Interestingly, treatment of 2,6-lutidyllithium with crotonaldehyde yielded only the alcohol corresponding to 1,2-addition with no Michael-type products being reported (8). We wish to report what we believe to be the first successful additions of the anions derived from 2- and 4-picoline to a Δ^1-butenolide and an α,β-unsaturated ketone to give monomeric products. While the yields of the reaction are admittedly low, we feel it significant that the reactions did proceed as one would expect.

The acidity of the α-hydrogen atoms of 2- and 4-picoline is widely recognized. We chose to use sodium amide as the base to generate **2** in our condensations. We were unable to observe addition products when sodium ethoxide was used to attempt to generate the anion and the use of alkyl- and aryllithiums resulted in the isolation of alkylated and arylated pyridine derivatives. 2(5*H*)Furanone (**1**, X = O) was prepared by the dehydrohalogenation of α-bromo-γ-butyrolactone (9). 2-Cyclopentenone (**1**, X = CH_2) was obtained commercially. The addition was most conveniently followed from examination of the ir spectra. 2(5*H*)Furanone contains a characteristic doublet carbonyl peak at 1783 and 1750 cm^{-1} while the addition products contain a singlet saturated carbonyl peak at 1775 cm^{-1}. Likewise, 2-cyclopentenone contains a signal at 1715 cm^{-1} corresponding to the unsaturated carbonyl group while the addition products contained a peak at 1740-1745 cm^{-1} for the saturated ketone. The nmr spectra and elemental analyses were consistent with the structures of the addition products (see Experimental).



1 X = O or CH_2 — **2** R = 2- or 4-pyridyl — **3**

a) X = O, R = 2-pyridyl
b) X = O, R = 4-pyridyl
c) X = CH_2, R = 2-pyridyl
d) X = CH_2, R = 4-pyridyl

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were determined on a Jeolco Model C-60-HL spectrometer. Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Dr. A. Bernhardt, Microanalytisches Laboratorium, Max Planck Institute fur Kohlenfurschung, Mulheim (Ruhr), West Germany. Sodium amide was prepared from sodium metal in liquid ammonia using Ferric chloride as a catalyst. The ammonia was evaporated and the sodium amide suspended in ether.

Dihydro-4-[2-pyridylmethyl]-2-(3*H*)furanone (**3a**).

A solution of 4.6 g. (0.05 mole) of 2-picoline in 50 ml. of ether was added to a suspension of sodium amide (prepared from 1.15 g. of sodium) in 150 ml. of ether over a period of 30 minutes. The mixture was refluxed for 45 minutes, cooled to room temperature and a solution of 4.2 g. (0.05 mole) of 2(5*H*)furanone (9) in 50 ml. of ether was added. The mixture was stirred overnight at room temperature, refluxed an additional 2 hours and cooled. The reaction was quenched by the addition of 50 ml. of water followed by 200 ml. of dilute (1:1) hydrochloric acid and the reaction mixture extracted with ether. The acidic layer was rendered alkaline with sodium carbonate and extracted with chloroform. The chloroform extracts were dried (magnesium sulfate) and evaporated to give 6.2 g. of a red-brown oil. Unreacted 2-picoline was removed by distillation at reduced pressure. The residue was purified by chromatography on neutral alumina (Brockman Activity I) using chloroform as eluting solvent to give 1.65 g. (19%) of **3a** as an oil; picrate (ethanol m.p. 86-88°; ir (liquid film) 1775 cm^{-1} (C = O saturated γ-lactone), 1595 and 1560 cm^{-1} (C = C and C = N of pyridine ring); nmr (deuterio-

chloroform) δ 2.03-2.66 (complex multiplet, 5H), 4.33 (t, 2, CH_2-O), 7.50 (m, 2, H_3 and H_5 pyridine ring); 7.83 (m, 1, H_4 pyridine ring); and 8.61 (m, 1, H_3 pyridine ring).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.82; H, 6.28; N, 7.95.

Dihydro-4-[4-pyridylmethyl]-2(3*H*)furanone (**3b**).

This compound was prepared by the same procedure used to prepare **3a** employing 4.6 g. (0.05 mole) of 4-picoline. After working-up the reaction as previously described and removing the unreacted 4-picoline, the residue was purified by chromatography on neutral alumina (Brockman Activity I) using chloroform as eluting solvent. Thus, **3b** was obtained (1.2 g., 15%) as a pale yellow liquid; picrate (ethanol) m.p. 153-155° dec.; ir (liquid film) 1775 cm^{-1} (C = O saturated γ-lactone), 1600 and 1580 cm^{-1} (C=C and C=N pyridine ring); nmr (deuteriochloroform) δ 2.10-2.56 (complex multiplet, 5H), 4.35 (t, 2, CH_2-O), 7.9 (m, 2, aromatic H_3 and H_5), and 9.0 (m, 2, aromatic H_2 and H_6).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.65; H, 6.37; N, 8.09.

3-(2-Pyridylmethyl)cyclopentanone (**3c**).

Following the procedure used to prepare **3a**, 4.6 g. (0.05 mole) of 2-picoline, 4.1 g. (0.05 mole) of 2-cyclopentenone, and sodium amide (prepared from 1.15 g. of sodium metal) were combined in ether. After working-up the reaction as previously described and removing the unreacted 2-picoline, the residue solidified and was recrystallized from acetone-petroleum ether to give 730 mg. (9%) of **3c**, m.p. 174-176° dec.; ir (chloroform) 1745 cm^{-1} (C=O saturated 5-membered cyclic ketone), 1600 and 1580 cm^{-1} (C=C and C=N pyridine ring); nmr (deuteriochloroform) δ 1.83-2.40 (m, 9H), 7.50 (m, 2, pyridine H_3 and H_5), 7.83 (m, 1, pyridine H_4), and 8.6 (m, 1, pyridine H_6).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.33; H, 7.37; N, 7.88.

3-(4-Pyridylmethyl)cyclopentanone (**3d**).

Following the procedure used to prepare **3c**, but using 4.6 g. (0.05 mole) of 4-picoline, the residue remaining after work-up and removal of unreacted 4-picoline solidified. Recrystallization from acetone-petroleum ether gave 1.2 g. (14%) of **3d**, m.p. 219-221°; ir (potassium bromide) 1740 cm^{-1} (C=O saturated 5-membered cyclic ketone), 1600 and 1550 cm^{-1} (C=C and C=N pyridine ring); nmr (deuteriochloroform) δ 1.83-2.40 (m, 9H), 7.66 (m, 2, pyridine H_3 and H_5), and 8.96 (m, 2, pyridine H_2 and H_6).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.31; H, 7.61; N, 8.05.

REFERENCES

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(2) Taken in part from the dissertation presented by H. Y. Aboul-Enein, July, 1971, to the Graduate School, University of Mississippi, in partial fulfillment of the requirements fro the Doctor of Philosophy Degree.

(3) N. A. Dryamova, S. I. Zav'yalov, and N. A. Preobrazhenskii, *J. Gen. Chem. U.S.S.R.*, **18**, 1733 (1948); through *Chem. Abstr.*, 43, 2625 (1949).

(4a) J. B. Jones and J. M. Young, *J. Med. Chem.*, **11**, 1176 (1968); (b) J. B. Jones and J. M. Young, *Can. J. Chem.*, **44**, 1059 (1966).

(5a) N. J. Leonard and J. H. Boyer, *J. Am. Chem. Soc.*, 72, 4818 (1950); (b) B. Magnus and R. Levine, *J. Org. Chem.*, **22**, 270 (1957); (c) J. Nichalski and H. Zajac, *J. Chem. Soc.*, 593 (1963).

(6) M. J. Weiss and C. R. Hauser, *J. Am. Chem. Soc.*, **71**, 2026 (1949).

(7a) H. Beyer and K. Levernenz, *Chem. Ber.*, **94**, 263 (1961); (b) H. Beyer, W. Lassig, and G. Schudy, *ibid.*, **90**, 592 (1957).

(8) V. Boekelheide, H. Fritz, J. M. Ross, and H. X. Haempfen, *Tetrahedron*, **20**, 33 (1964).

(9) C. C. Price and J. M. Judge, *Org. Syn.*, **45**, 22 (1965).