Novel Heterocycles. 6. The Condensation of Ethyl *o*-Fluorobenzoyl Acetate with Cyclic Imino Ethers

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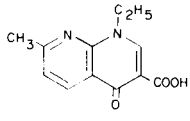
Received June 4, 1980

The reaction between ethyl *o*-fluorobenzoylacetate and cyclic imino ethers is described. The products, the corresponding 1,2-fused quinolines (**13a-17a**), were isolated in good yields. In one instance the uncyclized condensation intermediate **18** was isolated and characterized.

J. Heterocyclic Chem., **17**, 1729 (1980).

It has been shown that nalidixic acid (**1**) (1), oxolinic acid (**2**) (2) and piromidic acid (**3**) (3) exhibit antibacterial activity for gram-negative organisms. Nitrofurylvinyl 1,8-naphthyridine (**4**) possesses activity against both gram-negative and gram-positive bacteria (4).



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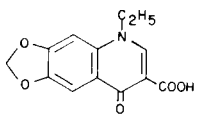

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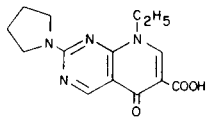

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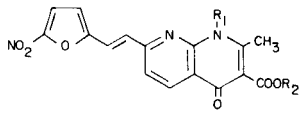
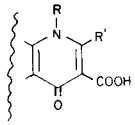


4a R_1 = H, R_2 = H

b R_1 = CH_3, R_2 = H

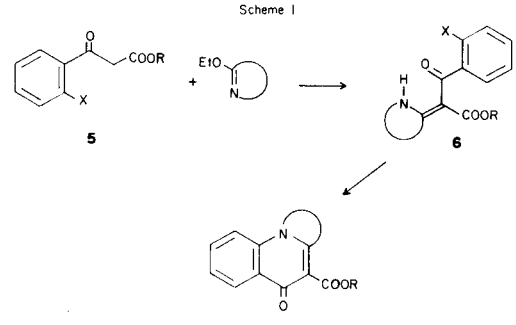
The common feature of these compounds is the 1,4-dihydro-4-oxonicotinic acid moiety which is fused at the 5 and 6 position.



We were interested in the possibility of preparing polycyclic compounds that were bridged between the nitrogen and the 2-position of the fused nicotinic acid. The synthetic approach that was chosen involves the reaction of a cyclic imino ether with a suitable active methylene compound which contains an appropriate functionality capable of promoting cyclization to furnish the products **7** (Scheme I).

Imino ethers have been reported to react with such active methylenes as ethyl cyanoacetate (5), methyl acetoacetate (6), and dimethyl acetonedicarboxylate (7). An analogous reaction with ethyl *o*-fluorobenzoylacetate (**5**, X = F, R = C_2H_5) would be expected to give compounds of type **6** which could then be cyclized by nucleophilic displacement of the activated fluorine to furnish **7**.

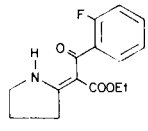
Scheme I



5 6 7

When ethyl *o*-fluorobenzoylacetate was allowed to react neat with imino ethers **8-12**, the cyclized products **13a-17a** were isolated directly in good yields (Scheme II). In general the reaction times varied between three and four days except in the case of **16a** where 17 days were needed to drive the reaction to completion.

In only one case was an intermediate of type **6** isolated. It was formed in the reaction of ethyl *o*-fluorobenzoylacetate with **8** where a mixture of **18** and **13a** resulted (8).



18

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian T-60 and EM 360 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrometer.

Imino ethers were prepared according to previously published methods: **8** (9); **9**, **10** (5,9); **12** (10).

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate.

No attempt has been made to optimize the yields of the described reactions.

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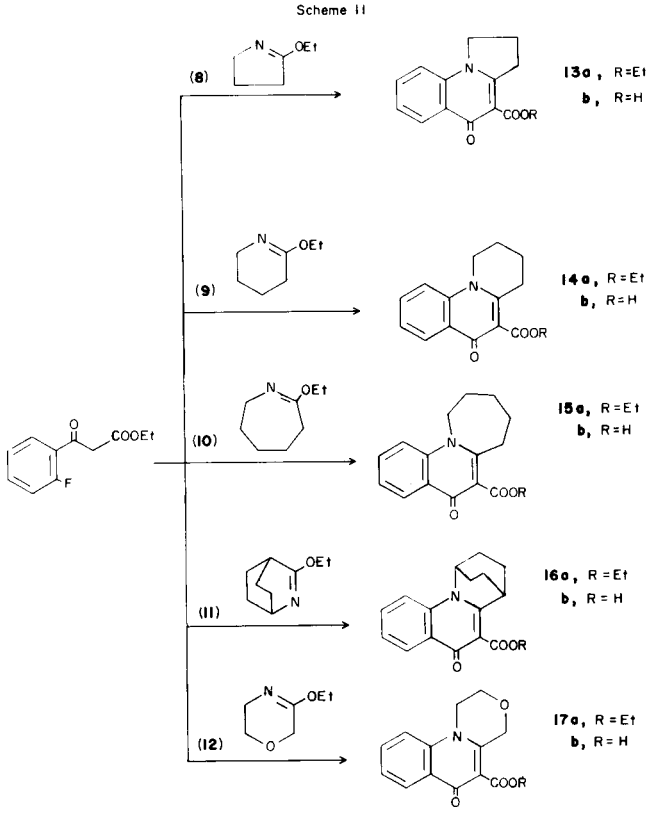
Scheme II



3-Ethoxy-2-azabicyclo[2.2.2]oct-2-ene (**11**).

To a solution of 30.5 g. of triethyloxonium tetrafluoroborate (11) in 300 ml. of methylene chloride was added dropwise a solution of 20 g. of 2-azabicyclo[2.2.2]octan-3-one (12) and the mixture was stirred at room temperature for 2 hours. It was then poured into cold 2*N* sodium carbonate, extracted into additional methylene chloride, and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting liquid was distilled at 10 mm in a Kugelrohr apparatus to give 20 g. (82%) of **11**; ir (chloroform): 1640 cm^{-1}; nmr (deuteriochloroform); δ 4.1 (q, 2), 3.95 (m, 1), 2.5 (m, 1), 1.55 (m, 8), 1.3 (t, 3).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.5; H, 9.9; N, 9.1. Found: C, 69.9; H, 10.2; N, 8.8.

Reanalysis of carbon did not improve the value.

General Procedure for the Preparation of Compounds **13a-17a**.

A mixture of 0.1 mole of ethyl *o*-fluorobenzoylacetate and 0.11 mole of the appropriate imino ether was stirred at 110-115° for three days. The mixture was allowed to cool and the residue was chromatographed on a column of silica gel using a solution of 2% methanol/chloroform to elute the product. Crystallization from ether furnished an analytical sample.

1,2,3,4-Tetrahydro-5-oxopyrrolo[1,2-*a*]quinoline-4-carboxylic Acid Ethyl Ester (**13a**).

Compound **13a** was obtained in 56% yield, m.p. 140-142°; ir (chloroform): 1700, 1615 cm^{-1}; nmr (deuteriochloroform): δ 8.3 (m, 1), 7.8-7.0 (m, 3), 4.4 (q, 2), 4.2 (t, 2), 3.4 (t, 2), 2.35 (m, 2), 1.4 (t, 3); ms: molecular ion at m/e 257.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.9; N, 5.4. Found: C, 70.2; H, 6.3; N, 5.3.

2,3,4,6-Tetrahydro-6-oxo-1*H*-benzo[*c*]quinolizine-5-carboxylic Acid Ethyl Ester (**14a**).

Compound **14a** was obtained in 90% yield, m.p. 132-135°; ir (chloroform): 1715, 1610 cm^{-1}; nmr (deuteriochloroform): δ 8.45 (m, 1), 7.8-7.1 (m, 3), 4.45 (q, 2), 4.05 (t, 2), 2.95 (t, 2), 1.95 (m, 4), 1.4 (t, 3).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.8; H, 6.3; N, 5.2. Found: C, 70.4; H, 6.5; N, 5.2.

5,7,8,9,10,11-Hexahydro-5-oxoazepino[1,2-*a*]quinoline-6-carboxylic Acid Ethyl Ester (**15a**).

Compound **15a** was obtained in 97% yield, m.p. 146-148°; ir (chloroform): 1715, 1610 cm^{-1}; nmr (deuteriochloroform): δ 8.4 (m, 1), 7.8-7.1 (m, 3), 4.35 (q, 2), 4.25 (m, 2), 2.9 (m, 2), 1.75 (s, broad, 6), 1.35 (t, 3).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.6; H, 6.7; N, 4.9. Found: C, 71.6; H, 6.9; N, 4.9.

2,3,4,6-Tetrahydro-6-oxo-1,4-ethano-1*H*-benzo[*c*]quinolizine-5-carboxylic Acid Ethyl Ester (**16a**).

Compound **16a** was obtained in 31% yield, m.p. 134-136°; ir (chloroform): 1725, 1620 cm^{-1}; nmr (deuteriochloroform): δ 8.5 (m, 1), 7.8-7.1 (m, 3), 5.1 (m, 1), 4.4 (q, 2), 3.5 (m, 1), 1.9 (m, 8), 1.4 (t, 3).

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.5; N, 4.7. Found: C, 73.1; H, 6.7; N, 4.7.

1,2,4,6-Tetrahydro-6-oxo[1,4]oxazino[4,3-*a*]quinoline-5-carboxylic Acid Ethyl Ester (**17a**).

Compound **17a** was obtained in 47% yield, m.p. 148-150°; ir (chloroform): 1715, 1625 cm^{-1}; nmr (deuteriochloroform): δ 8.3 (m, 1), 7.8-7.1 (m, 3), 4.85 (s, 2), 4.4 (q, 2), 4.1 (m, 4), 1.4 (t, 3).

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.9; H, 5.5; N, 5.1. Found: C, 65.7; H, 5.6; N, 5.1.

General Procedure for the Hydrolysis of Esters.

A suspension of 0.01 mole of the ester **13a-17a** in 50 ml. of 2*N* aqueous sodium hydroxide was refluxed for 1.5 hours. The resulting solution was cooled then acidified with 2*N* hydrochloric acid. The resulting precipitate was filtered, washed with water, and dried *in vacuo*. These products were found to be essentially analytically pure.

1,2,3,4-Tetrahydro-5-oxopyrrolo[1,2-*a*]quinoline-4-carboxylic Acid (**13b**).

Compound **13b** was obtained in 75% yield, m.p. 252-254°; ir (potassium bromide): 1710, 1610 cm^{-1}; nmr (DMSO-d_6): δ 8.35 (m, 1), 8.0-7.4 (m, 3), 4.5 (t, 2), 3.7 (t, 2), 2.3 (m, 2).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.1; H, 4.8; N, 6.1. Found: C, 67.7; H, 4.9; N, 6.3.

2,3,4,6-Tetrahydro-6-oxo-1*H*-benzo[*c*]quinolizine-5-carboxylic Acid (**14b**).

Compound **14b** was obtained in 92% yield, m.p. 255-258°; ir (potassium bromide): 1695, 1600 cm^{-1}; nmr (DMSO-d_6): δ 8.4 (m, 1), 8.1-7.4 (m, 3), 4.4 (t, 2), 3.7 (t, 2), 1.9 (m, 4).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.1; H, 5.4; N, 5.8. Found: C, 69.1; H, 5.7; N, 5.8.

5,7,8,9,10,11-Hexahydro-5-oxoazepino[1,2-*a*]quinoline-6-carboxylic Acid (**15b**).

Compound **15b** was obtained in 65% yield, m.p. 193-196°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.9; N, 5.4. Found: C, 69.8; H, 5.8; N, 5.8.

2,3,4,6-Tetrahydro-6-oxo-1,4-ethano-1*H*-benzo[*c*]quinolizine-5-carboxylic Acid (**16b**).

Compound **16b** was obtained in 81% yield, m.p. 227-228°; ir (potassium bromide): 1700, 1615 cm^{-1}; nmr (DMSO-d_6): δ 12.6 (s, broad, 1), 8.6-7.4 (m, 4), 5.7 (m, 1), 5.4 (m, 1), 1.9 (m, 8); ms: molecular ion at m/e 269.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.4; H, 5.6; N, 5.2. Found: C, 70.9; H, 5.6; N, 5.3.

Reanalysis of carbon did not improve the value.

1,2,4,6-Tetrahydro-6-oxo[1,4]oxazino[4,3-*a*]quinoline-5-carboxylic Acid (**17b**).

This compound was obtained in 75% yield, m.p. 263-266°.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.5; N, 5.7. Found: C, 63.4; H, 4.9; N, 5.8.

α-(2-Fluorobenzoyl)pyrrolidine-$\Delta^{2,\alpha}$-acetic Acid Ethyl Ester (**18**).

The reaction was performed as described in the general procedure for the preparation of **13a**. The residue was chromatographed on a column of silica gel using a solution of 2% methanol/chloroform to elute the product (the less polar fraction), 5.0 g. of **18** (44%). An analytical sample was crystallized from ether/pentane, m.p. 80-84°; ir (chloroform): 1680 cm^{-1}; nmr (deuteriochloroform): δ 10.6 (m, 1), 7.8-6.8 (m, 4), 3.9 (q, 2), 3.7 (t, 2), 3.3 (t, 2), 2.15 (m, 2), 0.85 (t, 3).

Anal. Calcd. for $C_{15}H_{16}FNO_3$: C, 65.0; H, 5.8; N, 5.1. Found: C, 65.4; H, 6.0; N, 5.0.

Acknowledgement.

The authors wish to thank Dr. Sandor Barcza and his associates for ir and nmr spectra, Mr. Robert Clark for measuring the mass spectra, and Mr. William Bonkoski and associates for performing the microanalyses.

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(8) Compound **18** is drawn as the *E*-isomer however the presence of the *Z*-isomer cannot be ruled out.

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