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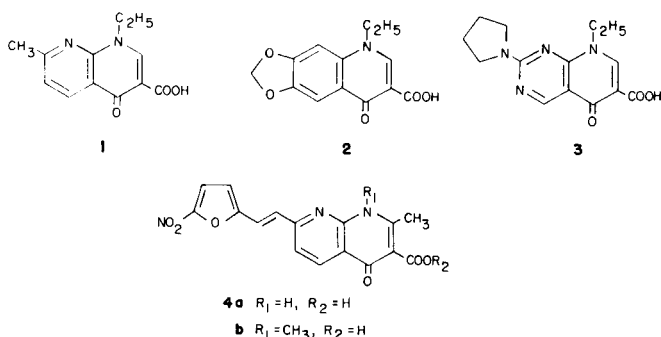
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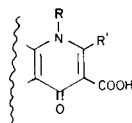
The reaction between ethyl *o*-fluorobenzoylacetate and cyclic imino ethers is described. The products, the corresponding 1,2-fused quinolines (**13a-17a**), were isolated in good yields. In one instance the uncyclized condensation intermediate **18** was isolated and characterized.

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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).

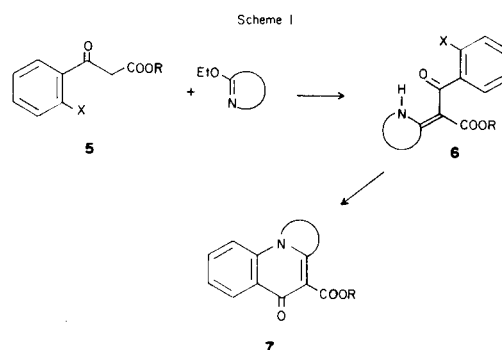


The common feature of these compounds is the 1,4-dihydro-4-oxonicotinic acid moiety which is fused at the 5 and 6 position.



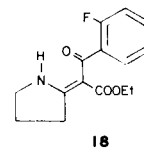
We were interested in the possibility of preparing polycyclic compounds that were bridged between the nitrogen and the 2-position of the fused nicotinic acid. The synthetic approach that was chosen involves the reaction of a cyclic imino ether with a suitable active methylene compound which contains 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 = C₂H₅) would be expected to give compounds of type **6** which could then be cyclized by nucleophilic displacement of the activated fluorine to furnish **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).



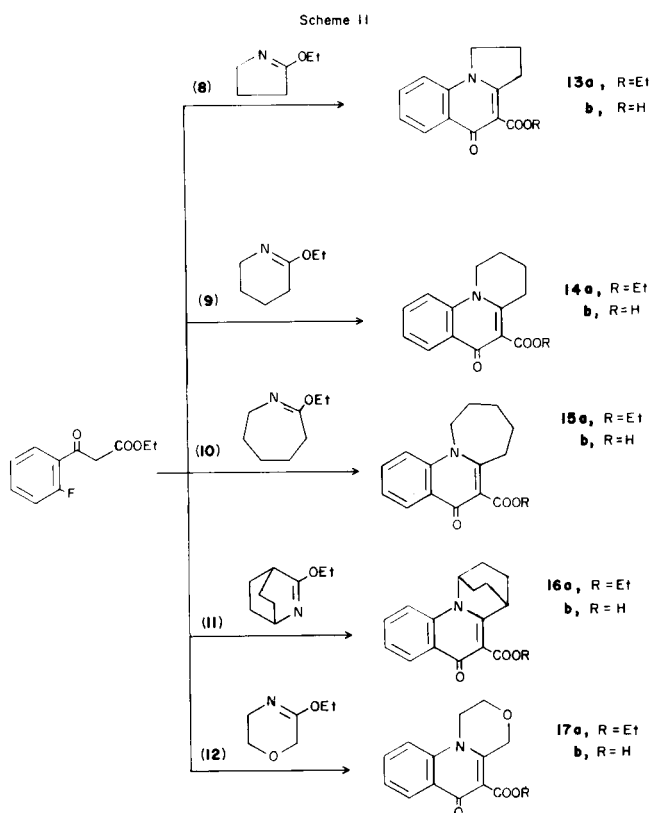
EXPERIMENTAL

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.



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 $\text{C}_9\text{H}_{13}\text{NO}$: 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 $\text{C}_{15}\text{H}_{19}\text{NO}_3$: 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 $\text{C}_{16}\text{H}_{17}\text{NO}_3$: 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 $\text{C}_{17}\text{H}_{19}\text{NO}_3$: 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 $\text{C}_{18}\text{H}_{19}\text{NO}_3$: 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 $\text{C}_{15}\text{H}_{15}\text{NO}_4$: 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 $\text{C}_{13}\text{H}_{11}\text{NO}_3$: 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 $\text{C}_{14}\text{H}_{13}\text{NO}_3$: 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 $\text{C}_{15}\text{H}_{15}\text{NO}_3$: 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 $\text{C}_{16}\text{H}_{15}\text{NO}_3$: 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 $C_{13}H_{10}FNO_3$: C, 65.0; H, 5.8; N, 5.1. Found: C, 65.4; H, 6.0; N, 5.0.

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