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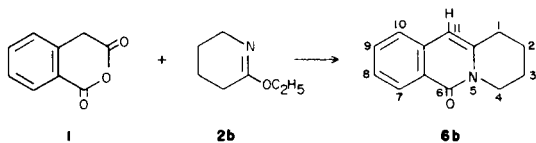
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Homophthalic anhydride and cyclic imino ethers react to produce fused isoquinolines **6-9**. In the case of 2-ethoxy-2-oxazoline, a second compound whose structure is believed to be the spiro compound **10** was also isolated. Spectral data for these type systems are discussed.

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Homophthalic anhydride (1,3-isochromanedione) **1** has been used in the synthesis of various heterocycles. When treated with the Vilsmeier Reagent, *N*-methyl-1-(2*H*)isoquinolones are formed (1). Stereoselective reactions of homophthalic anhydride and aldehydes in the presence of basic catalysts to produce *trans*-3,4-disubstituted-3,4-dihydroisocoumarins have been reported (2). Schiff bases react with **1** to form 3,4-dihydro-1-(2*H*)isoquinolinones (**3**) in a highly stereospecific fashion to produce *trans* geometry at the 3- and 4-positions (4).

In a continuing search for compounds possessing pharmacological activity it was decided to explore the reaction of homophthalic anhydride with cyclic imino ethers. When a mixture of **1** and 2-ethoxy-3,4,5,6-tetrahydropyridine (**2b**) was refluxed in toluene for 24 hours, the benzo [*b*]quinolizine **6b** was isolated in 51% yield. The structure of **6b** was deduced based on the following spectral evidence; the infrared spectrum exhibited three pronounced absorptions at 1650, 1630 and 1600  $\text{cm}^{-1}$ . The band at 1650  $\text{cm}^{-1}$  is attributed to the lactam carbonyl while the absorptions at 1630 and 1600  $\text{cm}^{-1}$  may be assigned to alkene and aromatic stretching vibrations respectively. The nmr spectrum exhibits a multiplet (4 protons) at  $\delta$  1.85, a triplet (2 protons) at  $\delta$  2.8, attributable to a methylene adjacent to an olefin, and a triplet (2 protons) at  $\delta$  4.05 which is a methylene adjacent to an amide nitrogen. Patterns such as this suggest a fused piperidine type system. A singlet (1 proton) at  $\delta$  6.3 is consistent with the olefinic proton at the 11 position while a multiplet at  $\delta$  8.35 is assigned to the aromatic proton peri to the carbonyl. The carbon-13 nmr spectrum exhibits carbon shifts (see Experimental Section) amenable to structure **6b** and the mass spectrum produces a molecular ion at *m/e* 199 which also supports the proposed structure.

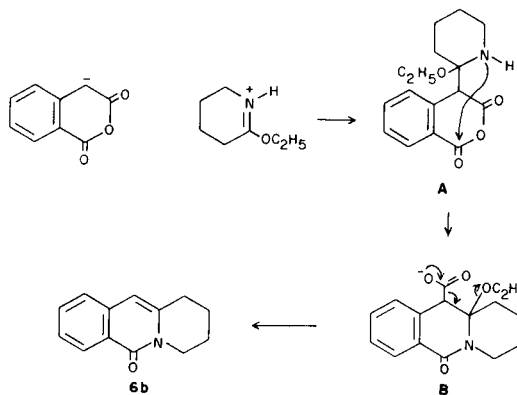


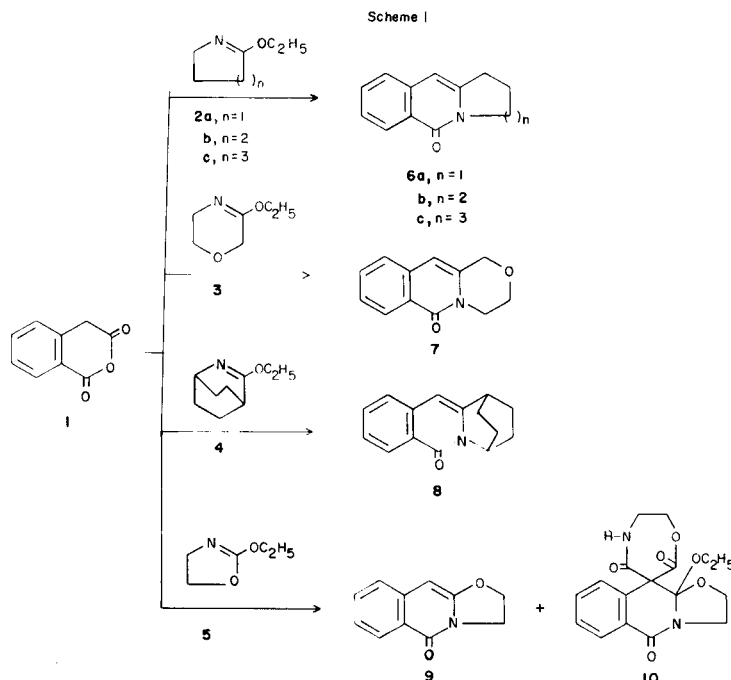
The moderate yield of the reaction prompted the investigation into the remainder of the reaction mixture.

Analysis indicated that approximately 30-40% of another product was present. It was found to be base soluble, suggesting that an acid functionality was present. The infrared spectrum (potassium bromide) exhibits four carbonyl absorptions at 1735, 1715, 1700 and 1685  $\text{cm}^{-1}$ . In the nmr spectrum, two overlapping triplets (3 protons) at  $\delta$  1.2 and 1.35 are seen while two singlets (2 protons) at  $\delta$  4.0 and two quartets (2 protons) at  $\delta$  4.35 and 4.1 are observed. The spectrum also exhibits a singlet (1 proton) at  $\delta$  11.8 which is exchangeable. The mass spectrum produces a molecular ion at *m/e* 208. This data along with corroborating elemental analysis indicates that the product is actually a mixture of monoethyl esters of homophthalic acid (**5**).



The formation of **6b** may possibly be explained by the mechanism outlined below. In the reaction medium, protonation of the imino ether by the homophthalic anhydride may occur generating the two charged species shown which can react to form intermediate **A**. Internal attack of the amine on the 1-carbonyl of the 1,3-isochromanedione may generate **B** which upon loss of carbon dioxide and ethoxide produces **6b**. A competing reaction of the generated ethoxide with **1** may also explain the formation of the monoethyl esters of homophthalic acid as major by-products.

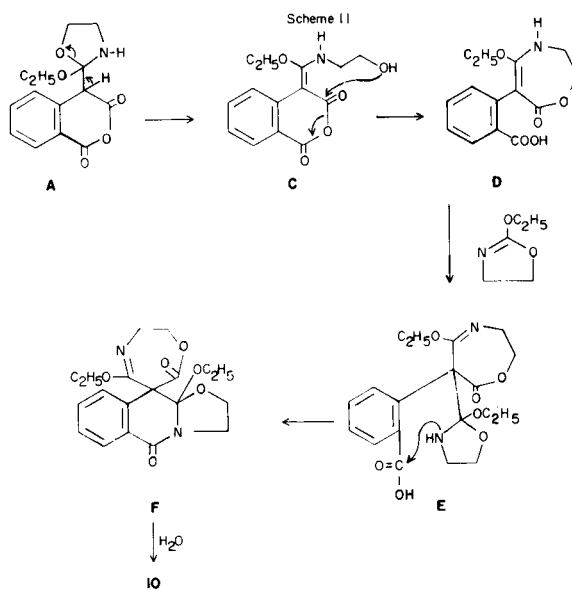




Analogous reactions were performed with homophthalic anhydride and a variety of cyclic imino ethers to generate an assortment of fused isoquinoline systems (Scheme I) with compounds **8** and **10** representing new ring systems.

In the reaction between 2-ethoxy-2-oxazoline (**5**) and **1**, the expected isoquinolone **9** was isolated in 20% yield. However, a second product, formed in approximately equal yield, was also isolated from the reaction mixture. Based upon the following data, the structure is believed to be **10**; the infrared spectrum exhibits absorptions at 3460 (N-H), 1720 (O-C=O) and 1655 (N-C=O)  $\text{cm}^{-1}$ . The band at 1655  $\text{cm}^{-1}$  is broadened, probably containing both amide frequencies. The presence of three carbonyl functionalities is also confirmed in the carbon-13 nmr spectrum, with signals being observed at 164.8, 159.6 and 157.8 ppm. The nmr spectrum reveals the presence of an ethoxy moiety with its characteristic quartet and triplet at  $\delta$  4.0 and 1.15. An exchangeable proton appears at  $\delta$  7.05 and three sets of multiplets ( $\delta$  4.8, 4.5-4.0, 3.4) integrating for 8 protons, 4 adjacent to an oxygen and 4 adjacent to a nitrogen, is observed. The mass spectrum produces a molecular ion at  $m/e$  346 (the molecular weight of **10**) and the elemental analysis is in full accord with the empirical formula.

The formation of **10** can be envisioned possibly by the mechanism proposed in Scheme II. An intermediate of Type **A** may form as previously mentioned. Subsequent ring opening to **C** and attack by oxygen on the 3-carbonyl of the isochromanedione may furnish **D**, which reacts with a second molecule of **5**. Internal cyclization of **E** could then result in the formation of **F** which, upon aqueous hydrolysis, furnishes **10**.



## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded 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.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on Varian XL-100-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. Sample concen-

trations were ca. 0.5 molar in deuteriodimethylsulfoxide in 10 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 5120 Hz; a pulse width of 25  $\mu$ , corresponding to a 43° pulse angle; and a pulse repetition time of 1.8 seconds. For all spectra 8K time-domain points were used. All shifts reported are referenced to internal TMS, and are estimated to be accurate to  $\pm$  0.05 ppm.

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.

#### 2-Ethoxy-2-oxazoline (5).

To a solution of 130.0 g. of triethylxonium tetrafluoroborate (6) in 350 ml. of methylene chloride was added dropwise a solution of 60.0 g. of 2-oxazolone in 300 ml. of methylene chloride and the mixture was stirred at room temperature for 3 hours. It was then poured into cold 2*N* sodium carbonate and the organic material was extracted into additional methylene chloride, and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was distilled at 1 mm on a Kugelrohr apparatus to give 38.5 g. (48%) of **5**, b.p. 30° (approximate), lit. (7) b.p. 96° (100 mm).

#### General Procedure for the Reaction of Homophthalic Anhydride with Imino Ethers.

A mixture of 0.05 mole of homophthalic anhydride and 0.055 mole of the appropriate imino ether (**2**, **3**, **4** or **5**) in 150 ml. of toluene was refluxed for 24 hours. The solvent was removed under reduced pressure and the residue dissolved in methylene chloride. The organic solution was washed with aqueous sodium bicarbonate and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to eluate the product. Using this procedure, the following compounds were prepared.

#### 2,3-Dihydropyrrolo[1,2-*b*]isoquinolin-5-(1*H*)one (6a).

The reaction of **1** and **2a** (**8**) under conditions described in the general procedure gave **6a** (44%) which was crystallized from ether/pentane, m.p. 94-96°; ir (chloroform): 1660, 1625, 1595  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  8.4 (m, 1), 7.8-7.2 (m, 3), 6.3 (s, 1), 4.15 (t, 2), 3.0 (t, 2); ms: (70 eV) *m/e* 185 ( $M^+$ ).

*Anal.* Calcd. for  $C_{12}H_{11}NO$ : C, 77.8; H, 6.0; N, 7.6. Found: C, 77.6; H, 6.3; N, 7.4.

#### 1,2,3,4-Tetrahydro-6*H*-benzo[*b*]quinolizin-6-one (6b).

The reaction of **1** and **2b** (**8,9**) under conditions described in the general procedure gave **6b** (51%), which was crystallized from ether/pentane, m.p. 100-103°; ir (potassium bromide): 1650, 1630, 1600  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  8.35 (m, 1), 7.8-7.2 (m, 3), 6.3 (s, 1), 4.05 (t, 2), 2.8 (t, 2), 1.85 (m, 4);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  163.1 (C=O), 141.3 (=C-N), 137.1 (C), 132.2 (C) arom,  $\delta$ , 128.0 (C) arom,  $\delta$ , 125.7 (C) arom,  $\delta$ , 125.3 (C) arom,  $\gamma$ , 124.6 (C-CO) arom, 103.9 (-CH=), 41.0 (N-CH<sub>2</sub>), 28.8 (=C-CH<sub>2</sub>), 22.4 (CH<sub>2</sub>), 19.1 (CH<sub>2</sub>); ms: (70 eV) *m/e* 199 ( $M^+$ ).

*Anal.* Calcd. for  $C_{13}H_{13}NO$ : C, 78.4; H, 6.6; N, 7.0. Found: C, 78.6; H, 7.0; N, 6.8.

The mixture of monoethyl esters of homophthalic acid may be obtained by acidifying the sodium bicarbonate washings.

#### 2,3,4,5-Tetrahydroazepino[1,2-*b*]isoquinolin-7-(1*H*)one (6c).

The reaction of **1** and **2c** (**8,9**) under conditions described in the general procedure gave **6c** (48%), which was crystallized from ether/pentane, m.p. 99-101°; ir (chloroform): 1650, 1625, 1600  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  8.4 (m, 1), 7.7-7.15 (m, 3), 6.25 (s, 1), 4.4 (m, 2), 2.75 (m, 2), 1.7 (s, broad, 6); ms: (70 eV) *m/e* 213 ( $M^+$ ).

*Anal.* Calcd. for  $C_{14}H_{15}NO$ : C, 78.8; H, 7.1; N, 6.6. Found: C, 79.1; H, 7.5; N, 6.5.

#### 3,4-Dihydro-1,4-oxazino[4,3-*b*]isoquinolin-6-(1*H*)one (7).

The reaction of **1** and **3** (**10**) under conditions described in the general procedure gave **7** (45%), which was crystallized from pentane, m.p. 87-90°; ir (chloroform): 1655, 1625, 1600  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  8.35 (m, 1), 7.8-7.15 (m, 3), 6.15 (s, broadened, 1), 4.6 (d, unresolved, 2), 4.0 (s, 4); ms (70 eV) *m/e* 201 ( $M^+$ ).

*Anal.* Calcd. for  $C_{12}H_{11}NO_2$ : C, 71.6; H, 5.5; N, 7.0. Found: C, 72.0; H, 5.5; N, 6.9.

#### 1,2,3,4-Tetrahydro-1,4-ethano-6*H*-benzo[*b*]quinolizin-6-one (8).

The reaction of **1** and **4** (**11**) under conditions described in the general procedure gave **8** (65%), which was crystallized from ether/pentane, m.p. 155-157°; ir (chloroform): 1655, 1620, 1600  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  8.45 (m, 1), 7.7-7.1 (m, 3), 6.3 (s, 1), 5.4 (m, 1), 2.9 (m, 1), 2.2-1.5 (m, 6); ms: (70 eV) *m/e* 225 ( $M^+$ ).

*Anal.* Calcd. for  $C_{15}H_{15}NO$ : C, 80.0; H, 6.7; N, 6.2. Found: C, 79.6; H, 6.6; N, 6.0.

#### 2,3-Dihydro-5*H*-oxazolo[3,2-*b*]isoquinolin-5-one (9).

The reaction of **1** and **5** under conditions described in the general procedure gave a mixture of **9** and **10**. The mixture was chromatographed on a column of silica gel using a solution of 2% methanol/chloroform to elute the products. Evaporation of the solvent of the fractions containing the less polar of the two products gave **9** (20%), which was crystallized from ether, m.p. 116-118°; ir (chloroform): 1670, 1630  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  8.25 (m, 1), 7.65-7.0 (m, 3), 5.8 (s, 1), 4.8-4.05 (m, 4); ms: (70 eV) *m/e* 187 ( $M^+$ ).

*Anal.* Calcd. for  $C_{11}H_9NO_2$ : C, 70.6; H, 4.9; N, 7.5. Found: C, 70.4; H, 4.5; N, 7.2.

#### 10'*a*-Ethoxy-2,3,3',4-tetrahydrospiro[2*H*,6*H*-oxazepine-6,10'(10'*a*)]-5*H*-oxazolo[3,2-*b*]isoquinoline-5,5',7'-trione (10).

Evaporation of the solvent of the fractions containing the more polar of the two products (from the column chromatography described above) gave **10** (19%); crystallized from methylene chloride/ether, m.p. 170-173°; ir (Nujol): 3460, 1720, 1655, 1600  $\text{cm}^{-1}$ ; nmr (DMSO-*d*<sub>6</sub>):  $\delta$  8.45 (m, 1), 8.05 (m, 1), 7.8-7.1 (m, 2), 7.05 (m, exchangeable, 1), 4.8 (m, 2), 4.5-4.0 (m, 4), 4.0 (q, 2), 3.4 (m, 2), 1.15 (t, 3);  $^{13}\text{C}$  nmr (DMSO-*d*<sub>6</sub>):  $\delta$  164.8 ( $\sum$  N-C=O), 159.6 (NH-C=O), 157.8 (O-C=O), 156.9 (C) arom, 136.7 (C-CO) arom, 133.5 (C) arom, 127.1 (C) arom, 124.7 (C) arom, 124.6 (C) arom, 121.5 (O-C-O), 85.2 (OC-C-CO), 69.7 (OCH<sub>2</sub>), 62.8 (OCH<sub>2</sub>, lactone), 59.9 (OCH<sub>2</sub>), 43.5 (N-CH<sub>2</sub>), 39.7 (NH-CH<sub>2</sub>), 14.7 (CH<sub>2</sub>-CH<sub>3</sub>); ms: (70 eV), *m/e* 346 ( $M^+$ ).

*Anal.* Calcd. for  $C_{17}H_{18}N_2O_6$ : C, 58.9; H, 5.2; N, 8.1. Found: C, 58.5; H, 5.3; N, 8.0.

#### Acknowledgment.

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