Synthesis of 7-Substituted 1*H*-Indolo[3,2-*d*][1,2]benzoxazepines

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The synthesis of the novel 7-substituted 1*H*-indolo[3,2-*d*][1,2]benzoxazepine ring system is described. Fischer indolization of 2-fluoroacetophenone phenylhydrazone provided the starting material 2-(2-fluorophenyl)-1*H*-indole. An acyl group was then introduced at the 3-position of the indole nucleus and the resulting ketone was converted to the ketoxime. Upon treatment with sodium hydride to form the oxanion of the ketoxime, an intramolecular cyclization took place *via* displacement of fluoride from the adjacent 2-fluorophenylsubstituent. This ring closure completed the construction of the 1*H*-indolo[3,2-*d*][1,2]benzoxazepine ring system.

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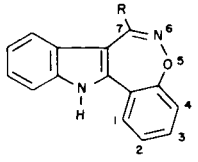
During recent years, we have maintained a strong interest in polynuclear heterocycles with potential biological activity. Previous reports from our laboratories have described the synthesis of spiro[isobenzofuran-1(3*H*),4'-piperidine]s [1,2], indolo[1,7-*ab*][1,5]benzodiazepines [3,4], and other polyheterocyclic systems [5] demonstrating antidepressant, diuretic and hypotensive properties. Continuing our investigations in this area, we now wish to report the synthesis of the novel 7-substituted 1*H*-indolo[3,2-*d*]-[1,2]benzoxazepine ring system **I**.

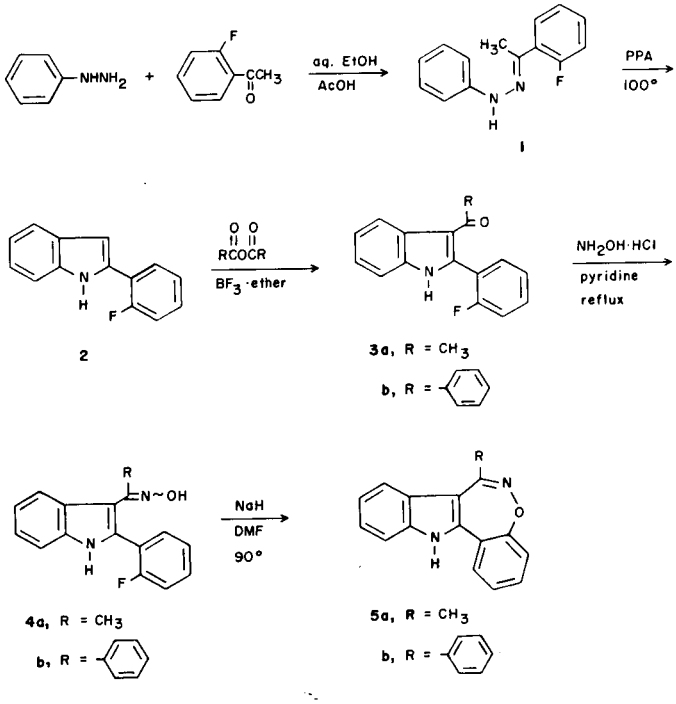


I

The starting material required for the synthesis (Scheme 1) was 2-(2-fluorophenyl)-1*H*-indole **2**. This compound was prepared in two steps *via* a Fischer indolization reaction. Phenylhydrazine was condensed with 2-fluoroacetophenone at room temperature in an ethanol-water solution to which several drops of acetic acid was added as catalyst. The resulting phenylhydrazone **1** was then smoothly cyclized to the desired indole **2** by heating in a polyphosphoric acid medium at 100° for 30 minutes. Next, an acyl group was introduced at the 3-position of the indole nucleus by reaction with an acid anhydride in the presence of boron trifluoride as catalyst.

Our strategy was to construct the seven-membered benzoxazepine ring by an intramolecular cyclization in which the oxanion of a ketoxime would displace fluoride from the nearby 2-fluorophenyl group. This methodology has been used frequently in these laboratories to synthesize novel ring systems [6-10]. Accordingly, ketone **3** was condensed with hydroxylamine hydrochloride in refluxing pyridine to provide the requisite oxime **4**. Whether R was methyl (**4a**) or phenyl (**4b**), a mixture of *syn* and *anti* isomers was obtained. Nevertheless, these oxime mixtures served well as the immediate precursors for the intramolecular cyclization reaction. When treated with sodium hydride in dimethylformamide to form the oxanion, oximes **4a** and **4b** readily cyclized by displacing fluoride from the adjacent phenyl ring. A reaction temperature of 90° for a short period of time (0.5-1 hour) was required to effect the cyclization. This process afforded the novel 1*H*-indolo-[3,2-*d*][1,2]benzoxazepine ring system bearing a 7-methyl (**5a**) or a 7-phenyl (**5b**) substituent.

Scheme I



Attempts to prepare the parent ring system (**5**, R = H) were not successful. The reaction conditions required for cyclization of the corresponding aldoxime resulted in opening of the benzoxazepine ring and formation of 3-cyano-2-(2-hydroxyphenyl)-1*H*-indole.

The novel 1*H*-indolo[3,2-*d*][1,2]benzoxazepines described in this report were screened for biological activity in a variety of pharmacological and biochemical tests. Except for a slight anxiolytic response observed at high doses for

5a and **5b** in the Geller-Conflict paradigm [11], no noteworthy biological activity was detected.

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Thomas-Hoover Uni-melt apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 grating spectrophotometer. Nuclear magnetic resonance spectra were taken at 60 MHz on a JEOL C-60HL spectrometer. Chemical shift values are reported in δ units (parts per million) relative to tetramethylsilane as an internal standard. Mass spectra were obtained from a Finnigan Model 4000 spectrometer interfaced to a Finnigan 9610 gas chromatograph and equipped with an INCOS data system. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Extraction solutions were dried over anhydrous sodium sulfate and were concentrated on a Buchi Rotavapor R. The final yields reported in this section represent analytically pure products. No effort was made to optimize yields.

1-(2-Fluorophenyl)ethanone Phenylhydrazone (**1**).

To a stirred solution, under nitrogen, of 48.5 g (0.35 mole) of 2-fluoroacetophenone and 39.6 g (0.37 mole) of phenylhydrazine in 220 ml of ethanol containing 90 ml of water was added 11 drops of glacial acetic acid as catalyst. After 2 hours at room temperature, the product which had separated as an oil was extracted into hexane (1 × 250 ml, 2 × 125 ml). The combined extracts were washed with 2*N* hydrochloric acid, with water and finally with brine before drying over anhydrous sodium sulfate. The solution was concentrated *in vacuo* to afford the phenylhydrazone as an oil weighing 71.8 g (89% yield). This material was somewhat unstable and therefore could not be purified further. It was, however, sufficiently pure by tlc to use as is in the next step; ir (chloroform): 3075-3000 (NH), 1680 (C=N), 1600, 1480, 1450 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.28 (d, C*H*$_3$, 3H), 6.85-7.92 (m, Ar*H*, 9H); ms: 229 ($M^+ + 1$).

2-(2-Fluorophenyl)-1*H*-indole (**2**).

A 1 liter resin flask, equipped with motor-drive stirrer, was charged with 500 ml of polyphosphoric acid (PPA). The acid was stirred and heated to 75° at which point 69.9 g (0.306 mole) of phenylhydrazone **1** was added. When the reaction temperature reached 100°, heating was discontinued. After 35 minutes, the hot mixture was poured into 3 liters of ice/water and then extracted with ether (3 × 1 liter). The ether extracts were combined, washed twice with water, then they were dried before concentration *in vacuo*. The resulting solid was boiled with 1.1 liters of hexane, filtered, and the filtrate was concentrated to dryness. The solid was triturated with hexane, filtered and dried to afford 44.4 g of indole, mp 96-98°. This was combined with a second crop of 4.65 g and recrystallized from 675 ml of hexane. After refrigeration overnight, the crystals were collected, washed with hexane, and dried. This provided 43.7 g (67.5% yield) of indole **2**, mp 97-98.5°, lit mp 97-98° [12].

1-[2-(2-Fluorophenyl)-1*H*-indol-3-yl]ethanone (**3a**).

To a solution of 8.49 g (0.04 mole) of indole **2** in 200 ml of chloroform containing 5.7 ml (0.06 mole) of acetic anhydride was added 9.8 ml (0.08 mole) of boron trifluoride etherate. After stirring at room temperature for 1 hour under nitrogen, the reaction mixture was partitioned between 400 ml of chloroform and 150 ml of concentrated ammonium hydroxide solution. After stirring vigorously for 15 minutes, the two phases were separated, and the aqueous phase was extracted with an additional 50 ml of chloroform. The combined chloroform extracts were washed twice with water, dried and concentrated to a solid weighing 9.2 g. This product was recrystallized from 150 ml of isopropanol to afford 5.26 g of pale yellow solid, mp 213° dec. A second crop of 2.01 g was obtained by concentration of the mother liquor and trituration of the resulting solid with isopropanol. The two crops were combined and recrystallized from 125 ml of ethanol to give 5.5 g (54.3%) of pale yellow crystals of **3a**, mp 213-215° dec; ir (potassium bromide): 3180-2950 (NH), 1620 (C=O), 1580, 1480, 1430 cm^{-1}; nmr (DMSO-d_6): δ 2.14 (s, C*H*$_3$, 3H), 7.20-8.42 (m, Ar*H*, 8H), 11.30 (N*H*, 1H); ms: m/e 253.

Anal. Calcd. for $C_{16}H_{12}FNO$: C, 75.87; H, 4.78; N, 5.53. Found: C, 76.13; H, 4.94; N, 5.64.

[2-(2-Fluorophenyl)-1*H*-indol-3-yl]phenylmethanone (**3b**).

A stirred solution of 5.20 g (24.6 mmoles) of indole **2** and 6.67 g (29.5 mmoles) of benzoic anhydride in 125 ml of chloroform was treated at room temperature under nitrogen with 4.5 ml (36.6 mmoles) of boron trifluoride etherate. The resulting mixture was refluxed for 5.5 hours, and then was cooled to room temperature and partitioned between 250 ml of chloroform and 100 ml of concentrated ammonium hydroxide solution. After 15 minutes of vigorous stirring, the phases were separated and the aqueous phase was extracted further with 50 ml of chloroform. The chloroform layers were combined and washed with water and with brine. Some undissolved product remained suspended in the chloroform phase and this was brought into solution by the addition of 200 ml of tetrahydrofuran. This organic solution was then dried and concentrated *in vacuo* to an orange solid. This crude product was triturated with a 1:1 ether:petroleum ether solution to afford 6.79 g of ketone, mp 217-219°. Recrystallization first from 500 ml of toluene, and then from 350 ml of ethanol furnished 4.97 g (64% yield) of pure **3b** in the form of orange needles, mp 228-229.5°; ir (potassium bromide): 3175-2900 (NH), 1590 (C=O), 1560, 1450, 1430 cm^{-1}; nmr (DMSO-d_6): δ 6.90-8.13 (m, Ar*H*, 13H), 12.02 (N*H*, 1H, exchangeable with deuterium oxide); ms: m/e 315.

Anal. Calcd. for $C_{21}H_{14}FNO$: C, 79.98; H, 4.47; N, 4.40. Found: C, 79.73; H, 4.57; N, 4.36.

1-[2-(2-Fluorophenyl)-1*H*-indol-3-yl]ethanone Oxime (**4a**).

A stirred mixture of 6.84 g (0.027 mole) of ketone **3a**, 18.8 g (0.27 mole) of hydroxylamine hydrochloride and 65 ml of pyridine in 65 ml of ethanol was refluxed under nitrogen for 2 hours. The reaction mixture was then cooled and partitioned between 500 ml of ether and 200 ml of 2*N* hydrochloric acid. The phases were separated and the organic layer was extracted with an additional 200 ml of 2*N* hydrochloric acid, and then it was washed twice with water before drying over anhydrous sodium sulfate. Concentration of this solution *in vacuo* left a yellow foam. This was triturated with 2:1 petroleum ether:ether solution to produce 6.2 g of beige solid. Recrystallization from 50 ml of toluene afforded 5.38 g (74% yield) of oxime **4a**, mp 135-149°; ir (potassium bromide): 3410, 3180-3075 (OH, NH), 1645 (C=N), 1620, 1580, 1490, 1460 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 2.05 (s, C*H*$_3$, 3H), 7.00-8.10 (m, Ar*H*, 8H), 9.96 (minor), 10.35 (major) (NO*H*, 1H, exchangeable with deuterium oxide), 11.08 (N*H*, 1H, exchangeable with deuterium oxide); ms: m/e 268.

This product was otherwise pure by tlc and was shown to be an approximately 2:1 isomeric mixture of *syn* and *anti* oximes. It was used as is in the cyclization step leading to **5a**.

[2-(2-Fluorophenyl)-1*H*-indol-3-yl)phenylmethanone Oxime (**4b**).

The same oximation procedure of the previous example was used to prepare oxime **4b** except that ketone **3b** was the starting material and the reflux period was 4.25 hours. The pure product, mp 160-163°, was obtained in 81% yield; ir (potassium bromide): 3240, 3060-2860 (OH, NH), 1620 (C=N), 1575, 1482, 1450 cm^{-1}; nmr (DMSO-d_6): δ 6.94-7.76 (m, Ar*H*, 13H), 10.30 (minor), 10.50 (major) (NO*H*, 1H, exchangeable with deuterium oxide), 11.08 (N*H*, 1H, exchangeable with deuterium oxide); ms: m/e 330.

This product was otherwise pure by tlc and was shown to be an approximately 3:1 isomeric mixture of *syn* and *anti* oximes. It was used as is in the cyclization step leading to **5b**.

7-Methyl-1*H*-indolo[3,2-*d*][1,2]benzoxazepine (**5a**).

To a stirred suspension of 1.37 g (0.057 mole) of sodium hydride in 100 ml of anhydrous dimethylformamide under nitrogen was added dropwise, over a 20 minute period, a solution of 7.05 g (0.026 mole) of oxime **4a** in 80 ml of dimethylformamide. After stirring for 20 minutes at room temperature, the mixture was heated to 90°. After 30 minutes at that

temperature, the mixture was cooled, treated with 500 ml of water, and extracted with ether (1 × 500 ml, 1 × 250 ml). The combined ether extracts were washed three times with water, once with brine and then dried before concentration to a foam weighing 2.81 g. This material was purified by preparative hplc using a single column and 5% ethyl acetate in toluene as eluant. The fractions containing the purified product were combined and concentrated *in vacuo*. The resulting foam was triturated to a crystalline solid with 2:1 petroleum ether:ether solution. This pure product **5a** was found to weigh 2.17 g (33% yield), mp 145°; ir (potassium bromide): 3215-3180 (NH), 1585 (C=N), 1560, 1500, 1440 cm^{-1}; nmr (deuteriochloroform): δ 2.56 (s, CH_3, 3H), 7.05-7.90 (m, Ar*H*, 8H), 9.72 (N*H*, 1H); ms: m/e 248.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.29. Found: C, 77.75; H, 4.87; N, 11.42.

7-Phenyl-1*H*-indolo[3,2-*d*][1,2]benzoxazepine (**5b**).

To a stirred suspension of 0.46 g (19.2 mmoles) of sodium hydride in 50 ml of anhydrous dimethylformamide under nitrogen was added dropwise, over an 8 minute period, a solution of 5.79 g (17.5 mmoles) of oxime **4b** in 80 ml of dimethylformamide. After stirring for 1 hour at room temperature, the reaction was heated at 85-90° for 1 hour. The mixture was then cooled, treated with 175 ml of water, and extracted with ether (1 × 350 ml, 1 × 175 ml). The combined ether extracts were washed twice with water, once with brine, and then dried over anhydrous sodium sulfate. Concentration of the solvent *in vacuo* afforded a crude solid which was triturated with 2:1 petroleum ether:ether solution to afford 4.75 g of product. This material was dissolved in 160 ml of boiling ethanol, filtered while hot, and the filtrate was boiled down to a volume of 100 ml at which point crystallization began to occur. The recrystallization mixture was allowed to cool to room temperature, and then was chilled in an ice-bath for 1 hour before the crystals were collected, washed well with ethanol, then with hexane. After drying, there was obtained 2.74 g (51% yield) of pure **5b**, mp 177°; ir (potassium bromide): 3240-3020 (NH), 1600 (C=N), 1575, 1530, 1480 cm^{-1}; nmr (DMSO-d_6): δ 6.60-8.22 (m, Ar*H*, 13H), 12.0 (N*H*, 1H); ms: m/e 310.

Anal. Calcd. for $C_{21}H_{14}N_2O$: C, 81.27; H, 4.55; N, 9.03. Found: C, 81.57; H, 4.74; N, 9.14.

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