

## Nucleophilic Displacement of Aromatic Fluorine, Part I, Synthesis of Benzisoxazoles

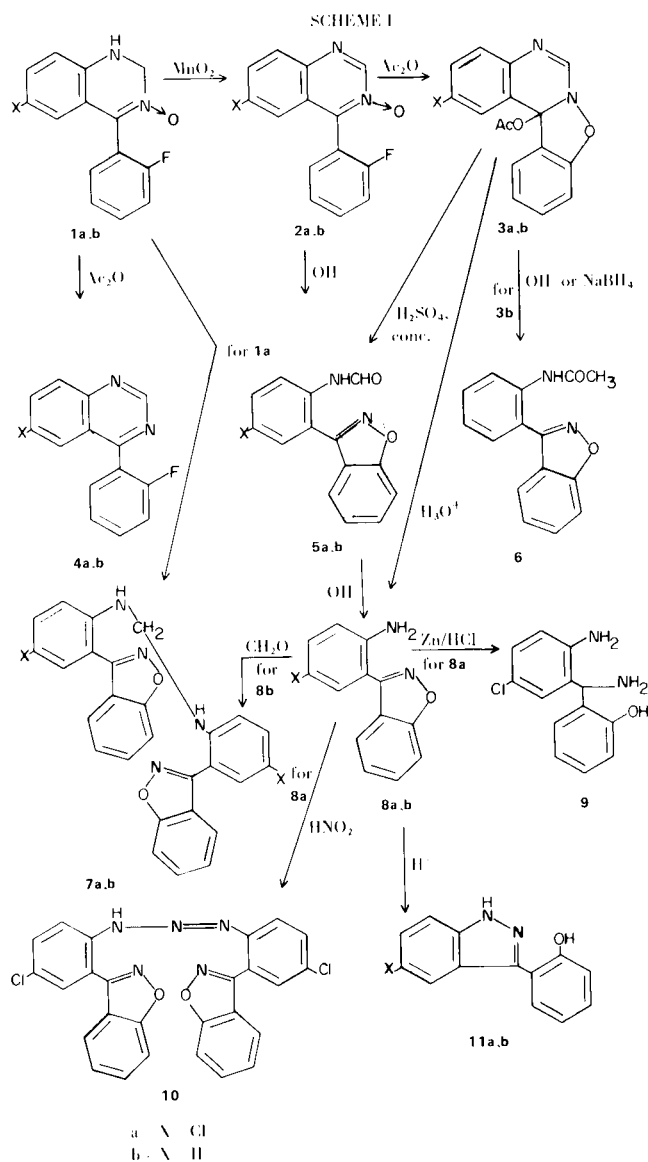
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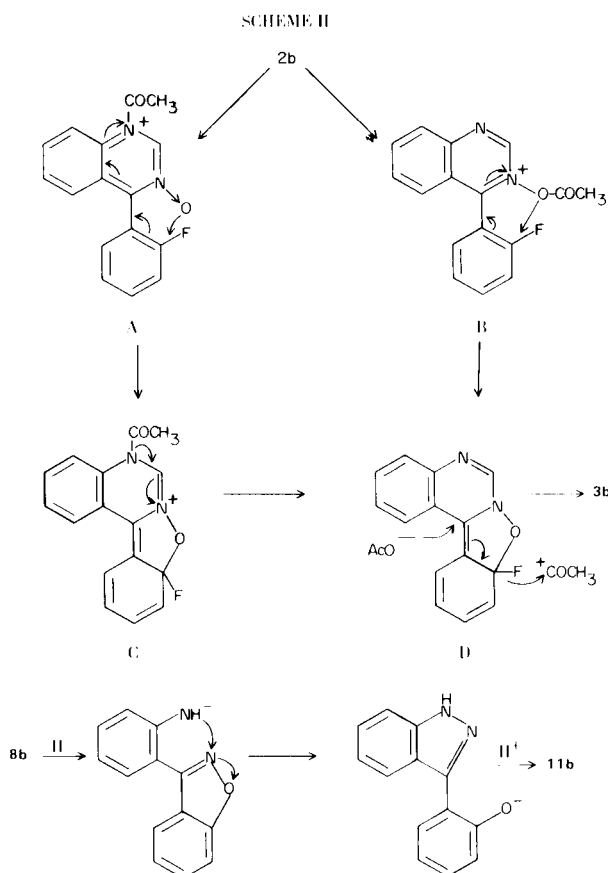
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The quinazoline 3-oxides **2** were found to convert to the benzisoxazoloquinazolines **3** by heating in acetic anhydride. The dihydroquinazoline 3-oxides **1** underwent aromatization to **4** under the same conditions. Hydrolysis of **3** or **2** led to the 3-(2-aminophenyl)benzisoxazoles **8** which could be rearranged to the 3-(2-hydroxyphenyl)indazoles **11** by treatment with hydride. Possible mechanisms are discussed.

The facile nucleophilic exchange of fluorine in nitroaromatic compounds has long been known. More recently it has been demonstrated that displacement of aromatic fluorine by amines also preceded when there was activation by other electron withdrawing substituents *e.g.*, a carbonyl function (**1**) or an *N*-oxide group (**2**). Intramolecular versions of this reaction have been applied to the synthesis of benzodiazepines (**3**), acridones (**4**) and tetrahydropyridoindoles (**5**). We now wish to report an unusual example of an intramolecular nucleophilic displacement of fluorine by oxygen in the quinazoline oxides **2** (Scheme I). The quinazolines **2** were conveniently prepared by the oxidation of the corresponding 1,2-dihydro derivatives **1** (**6**) with activated manganese dioxide. Treatment of compounds **2** with boiling acetic anhydride led in good yields to the crystalline products **3**. The structures assigned were based on the interpretation of the analytical and spectral data. Acid hydrolysis of these benzisoxazolo[2,3-*c*]quinazolines yielded the 3-(2-aminophenyl)benzisoxazoles **8**. The latter were also obtained by vigorous alkaline hydrolysis of the quinazoline 3-oxides **2**, while more controlled conditions allowed the isolation of the intermediate formyl derivatives **5**. Compound **5b** was also formed by the action of concentrated sulfuric acid on **3b**. Treatment of **3b** either with alcoholic sodium hydroxide or with sodium borohydride produced the acetanilide derivative **6**, possibly by an intramolecular transacetylation. The reduction of compound **3b** with lithium aluminum hydride at low temperature led to the aminal **7b** which, for purposes of comparison, was prepared in low yield by the reaction of **8b** with formaldehyde. The aminal **7a** was obtained in higher yield by the treatment of the dihydroquinazoline 3-oxide **1a** with potassium hydroxide. Boiling acetic anhydride converted the dihydroquinazolines **1** cleanly to the quinazolines **4**.





A plausible mechanism which would explain the formation of compounds **3** from the quinazoline 3-oxides **2** is shown in Scheme II. It is likely that acylation of either  $N_1$ -nitrogen (A) or the  $N$ -oxide (B) would increase the electrophilic character of the carbon atom bearing the fluorine. This would facilitate the formation of the carbon-oxygen bond and lead to intermediate D. Elimination of fluoride ion and incorporation of acetate as shown would then give **3b** and acetyl fluoride.

It was interesting to find that the attempted reduction of the benzisoxazole **8b** with lithium aluminum hydride in refluxing tetrahydrofuran resulted mainly in the isomerization of **8b** to the indazole **11b**. This novel ring transformation could be more effectively achieved by using sodium hydride instead of lithium aluminum hydride and was used for the preparation of **11a** and **11b**. The conversion of the benzisoxazole to the indazole is probably best represented by the mechanism depicted in Scheme II. The hydride is assumed to generate an anion by abstracting a proton from the primary amine. This anion would then attack intramolecularly the nitrogen of the benzisoxazole ring. Cleavage of the  $N$ -O bond would result in the formation of the more stable phenolate anion. Similar ring transformations involving nucleophilic attack on nitrogen have been reported in the literature (7).

Reductive ring opening of **8a** with zinc and hydrochloric acid yielded the benzhydramine **9**. Nitrosation of **8a** in glacial acetic acid gave the triazene **10**.

#### EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with Varian A-60 and T-60 instruments with TMS as internal standard. Ir spectra were determined on a Beckman ir-9 spectrometer and mass spectra were run on a CEC-110 B instrument.

Silica gel Merck (70-325 mesh) was used for chromatography, and anhydrous sodium sulfate for drying purposes.

#### 6-Chloro-4-(2-fluorophenyl)quinazoline 3-Oxide (**2a**).

A mixture of 138.3 g. (0.5 mole) of 6-chloro-1,2-dihydro-4-(2-fluorophenyl)quinazoline 3-oxide (**1a**) (6) 2.5 l. of methylene chloride and 400 g. of activated manganese dioxide was stirred at room temperature for 2½ hours. The manganese dioxide was removed by filtration over celite and was washed well with methylene chloride. The filtrate was evaporated and the crystalline residue was collected with ether to yield 116 g. (84.5%) of product with m.p. 198-201°. For analysis it was recrystallized from methylene chloride/methanol, m.p. 205-207°; uv:  $\lambda$  max 230  $m\mu$  ( $\epsilon = 23,600$ ) 306 (6,900) 363 (4,200) inf 381 (3,300).

*Anal.* Calcd. for  $C_{14}H_8ClFN_2O$ : C, 61.2; H, 2.9; N, 10.2. Found: C, 61.3; H, 2.7; N, 10.2.

#### 4-(2-Fluorophenyl)quinazoline 3-Oxide (**2b**).

Similarly, oxidation of 12.1 g. (0.05 mole) of 1,2-dihydro-4-(2-fluorophenyl)quinazoline 3-oxide (**1b**) with 60 g. of manganese dioxide in 500 ml. of methylene chloride yielded 7.7 g. (64%) of product with m.p. 156-158°. The analytical sample was recrystallized from methylene chloride/ethanol m.p. 157-159°; uv:  $\lambda$  inf 220  $m\mu$  ( $\epsilon = 20,000$ ) max 266 (27,400) 302 (7,600) 360 (4,220).

*Anal.* Calcd. for  $C_{17}H_9FNO_2$ : C, 70.0; H, 3.8; N, 11.7. Found: C, 69.9; H, 3.7; N, 11.8.

#### 12b-Acetoxy-2-chloro-1,2bH-[1,2]benzisoxazolo[2,3-c]quinazoline (**3a**).

A mixture of 55 g. (0.2 mole) of **2a** and 1 l. of acetic anhydride was heated to reflux for 5 hours. The reagent was removed under reduced pressure, at the end azeotropically with xylene. The crystalline residue was collected with ether to leave 58 g. (92%) of product with m.p. 180-182°. For analysis it was recrystallized from methylene chloride/ethanol; uv:  $\lambda$  max 286  $m\mu$  ( $\epsilon = 6,220$ ); ir (chloroform): 1730  $cm^{-1}$ , 1705  $cm^{-1}$  (CO); nmr (deuteriochloroform): 2.18 ppm (s, 3, COCH<sub>3</sub>) 7.1-7.9 (m, 7, aromatic H) 9.2 (s, 1, C-6-H); MS:  $m/e$  314 ( $M^+$ ), 286, 272, 255, 244, 216, 181, 152, 124, 43.

*Anal.* Calcd. for  $C_{16}H_{11}ClN_2O_3$ : C, 61.06; H, 3.52; N, 8.90. Found: C, 60.81; H, 3.44; N, 8.91.

#### 12b-Acetoxy-1,2bH-[1,2]benzisoxazolo[2,3-c]quinazoline (**3b**).

Treatment of 48 g. of **2b** with 500 ml. of acetic anhydride at reflux for 5 hours, yielded 43.5 g. of product with m.p. 108-112°, crystallized from ethanol. The analytical sample was recrystallized from methylene chloride/ethanol; uv:  $\lambda$  inf 230  $m\mu$  ( $\epsilon = 9,300$ ) max 286 (3,650), ir (chloroform): 1730  $cm^{-1}$ , 1705  $cm^{-1}$  (CO); nmr (deuteriochloroform):  $\delta$  2.15 ppm (s, 3, COCH<sub>3</sub>), 7.1-8 (m, 8, aromatic H) 9.3 (s, 1, C-6-H); MS:  $m/e$  280 ( $M^+$ ), 252, 238, 237, 222, 221, 211, 210, 182, 91, 43.

*Anal.* Calcd. for  $C_{16}H_{12}N_2O_3$ : C, 68.6; H, 4.3; N, 9.9. Found: C, 68.7; H, 4.4; N, 10.0.

6-Chloro-4-(2-fluorophenyl)quinazoline (**4a**).

A mixture of 5.47 g. (0.2 mole) of **1a**, 100 ml. of acetic anhydride was heated to reflux for 2½ hours. The reagent was removed under reduced pressure and the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization from methylene chloride/hexane yielded 3.2 g. (62%) of product with m.p. 116-118°. For analysis it was recrystallized from methylene chloride/2-propanol, m.p. 116-119°; uv:  $\lambda$  max 228 m $\mu$  ( $\epsilon = 49,100$ ) 263 (7,050) 323 (5,500); nmr (deuteriochloroform):  $\delta$  7-8.2 ppm (m, 7, aromatic H) 9.4 (s, 1, C<sub>2</sub>-H).

*Anal.* Calcd. for  $C_{14}H_8ClFN_2$ : C, 65.0; H, 3.1; N, 10.8. Found: C, 65.3; H, 2.9; N, 11.0.

4-(2-Fluorophenyl)quinazoline (**4b**).

Refluxing a mixture of 50 g. of **1b** and 500 ml. of acetic anhydride for 15 minutes yielded after the same workup and crystallization from methanol/water 37.4 g. (84%) with m.p. 81-84°. For analysis it was recrystallized from 2-propanol, m.p. 84-86°; uv:  $\lambda$  max 223 m $\mu$  ( $\epsilon = 36,500$ ) 257 (6,800) inf 275 (5,400) max 314 (5,400).

*Anal.* Calcd. for  $C_{14}H_9FN_2$ : C, 74.9; H, 4.1; N, 12.5. Found: C, 74.9; H, 3.9; N, 12.4.

3-(2-Formamido-5-chlorophenyl)-1,2-benzisoxazole (**5a**).

A mixture of 2.74 g. (0.01 mole) of **2a**, 10 ml. of 1 N potassium hydroxide solution and 100 ml. of ethanol was refluxed overnight. The usual workup and fractional crystallization from methylene chloride/2-propanol yielded 1 g. (37%) of product with m.p. 115-118°. For analysis it was recrystallized from methylene chloride/ethanol, m.p. 117-120°; ir (chloroform): 3350  $cm^{-1}$  (NH) 1700 (C=O).

*Anal.* Calcd. for  $C_{14}H_9ClN_2O_2$ : C, 61.6; H, 3.3; N, 10.3. Found: C, 61.1; H, 3.3; N, 10.2.

3-(2-Formamidophenyl)-1,2-benzisoxazole (**5b**).

A mixture of 1 g. of **3b** and 20 ml. of concentrated sulfuric acid was stirred overnight at room temperature. It was then poured on ice and the product was extracted with ether. The extracts were dried and evaporated. Crystallization of the residue from ether/hexane left 0.47 g. (55%) of product with m.p. 96-99°. The analytical sample was recrystallized from methylene chloride/ethanol, m.p. 98-100°; uv:  $\lambda$  sh 237 m $\mu$  ( $\epsilon = 23,500$ ) inf 246 (19,500) max 291 (7,900); ir (chloroform): 3350  $cm^{-1}$  (NH) 1700 (C=O).

*Anal.* Calcd. for  $C_{14}H_{10}N_2O_2$ : C, 70.6; H, 4.2; N, 11.8. Found: C, 70.5; H, 4.3; N, 11.9.

This compound was also obtained besides **8b** by treatment of **2b** with equimolar amounts of sodium hydroxide as described for the corresponding chloro derivative **5a**.

3-(2-Acetaminophenyl)-1,2-benzisoxazole (**6**).

A.

A mixture of 1.41 g. (0.005 mmole) of **3b**, 6 ml. of 1 N sodium hydroxide solution and 100 ml. of ethanol was heated to reflux overnight. The usual workup followed by crystallization from ether/hexane yielded 1 g. (79%) of product with m.p. 70-73°. For analysis it was recrystallized from the same solvents, m.p. 72-73°; uv:  $\lambda$  max 235 m $\mu$  ( $\epsilon = 20,700$ ) 290 (7,700); ir (chloroform): 3350  $cm^{-1}$  (NH) 1695  $cm^{-1}$  (C=O); nmr (deuteriochloroform): 2.16 ppm (s, 3, COCH<sub>3</sub>) 7-8 (m, 7, aromatic H) 8.6 (d, 1, J = 8 Hz, proton ortho to acetamido group) 9.9 (broad s, 1, NH).

*Anal.* Calcd. for  $C_{15}H_{12}N_2O_2$ : C, 71.4; H, 4.8; N, 11.1. Found: C, 71.2; H, 4.9; N, 11.1.

B.

A mixture of 2.8 g. (0.01 mole) of **3b**, 1.5 g. of sodium borohydride and 125 ml. of ethanol was stirred at room temperature for 2 hours. The product was extracted with methylene chloride after dilution with water. The extracts were dried and evaporated. Crystallization of the residue from ether/petroleum ether yielded 1.7 g. (67.5%) of material with m.p. and mixed m.p. identical with the above product.

Di-[4-Chloro-2-(3-benzisoxazolyl)anilino]methane (**7a**).

A mixture of 2.77 g. (0.01 mole) of **1a**, 1.7 g. (0.03 mole) of potassium hydroxide and 125 ml. of ethanol was stirred and heated to reflux overnight. After dilution with water, the product was extracted with methylene chloride. The extracts were dried and evaporated. Crystallization from methylene chloride/ethanol yielded 1.6 g. (63%) of colorless material with m.p. 171-174°. For analysis it was recrystallized from the same solvents; uv:  $\lambda$  max 233 m $\mu$  ( $\epsilon = 41,250$ ) inf 278 (13,750) inf 285 (11,000) sh 297 (7,600) 355 (10,150).

*Anal.* Calcd. for  $C_{27}H_{18}Cl_2N_4O_2$ : C, 64.7; H, 3.6; N, 11.2. Found: C, 64.5; H, 3.6; N, 11.2.

Di-[2-(3-benzisoxazolyl)anilino]methane (**7b**).

A.

Compound **3b**, 2.8 g. (0.01 mole), was added in portions to a suspension of 0.76 g. (0.02 mole) of lithium aluminum hydride in 150 ml. of tetrahydrofuran cooled to -20°. After stirring under nitrogen at -15° to -20° for 30 minutes, the reaction mixture was hydrolysed by addition of 4 ml. of water. The inorganic material was separated by filtration and the filtrate was dried and evaporated. Crystallization from ether yielded 0.7 g. (31%) of product with m.p. 160-163°. For analysis it was recrystallized from methylene chloride/ethylacetate, m.p. 161-163°; uv:  $\lambda$  max 235 m $\mu$  ( $\epsilon = 39,700$ ) 276 (9,400) 284 (9,100) 296 (8,600) 345 (10,600); ir (chloroform): 3375  $cm^{-1}$  (NH); nmr (DMSO):  $\delta$  4.86 (t, 2, J = 6 Hz, NHCH<sub>2</sub>-NH) 6,7-8, 2 (m, 18, aromatic H, NH).

*Anal.* Calcd. for  $C_{27}H_{20}N_4O_2$ : C, 74.9; H, 4.7; N, 12.9. Found: C, 74.8; H, 4.6; N, 12.7.

B.

A mixture of 1.05 g. (5 mmoles) of **8b**, 0.8 ml. of aqueous formaldehyde (30%) and 40 ml. of ethanol was heated to reflux overnight. After dilution with water, the product was extracted with ether. The extracts were dried and evaporated. Crystallization from ether/hexane yielded 0.2 g. (18.5%) of material which, after recrystallization from methylene chloride/ethyl acetate, had m.p. and mixed m.p. identical with those of the above product.

3-(2-Amino-5-chlorophenyl)-1,2-benzisoxazole (**8a**).

A.

A mixture of 5.5 g. (0.02 mole) of **2b**, 20 ml. of 3 N potassium hydroxide solution and 100 ml. of ethanol was heated to reflux overnight. The cold reaction mixture was diluted with water and extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from methylene chloride/ethanol yielded 3.7 g. (75.5%) of product with m.p. 117-120°; uv:  $\lambda$  max 225 m $\mu$  ( $\epsilon = 21,200$ ) 234 (21,700) 278 (5,350) inf 287 (4,600) 297 (3,600) 353 (5,200); nmr (deuteriochloroform):  $\delta$  5.03 ppm (broad s, 2, NH<sub>2</sub>) 6, 7 (d, 1, J = 9 Hz, proton ortho to -NH<sub>2</sub>) 7-8 (m, 6, aromatic H).

*Anal.* Calcd. for  $C_{18}H_9ClN_2O$ : C, 63.8; H, 3.8; N, 11.4. Found: C, 63.8; H, 3.8; N, 11.4.

B.

A mixture of 31.5 g. (0.1 mole) of **3a**, 100 ml. of 3*N* hydrochloric acid and 500 ml. of ethanol was heated to reflux overnight. After dilution with ether, the mixture was extracted with methylene chloride. The extracts were dried and evaporated. Crystallization from methylene chloride/ethanol yielded 15 g. (61.5%) of product with m.p. 118-120°.

3-(2-Aminophenyl)-1,2-benzisoxazole (**8b**).

Refluxing a mixture of 28 g. (0.1 mole) of **3b**, 500 ml. of 3*N* hydrochloric acid and 1.5 l. of ethanol overnight produced after the usual workup and crystallization from methylene chloride/ethanol 16.4 g. (78%) of product with m.p. 106-108°; uv:  $\lambda$  max 234  $m\mu$  ( $\epsilon = 19,400$ ) 277 (4,250) 284 (4,300) 295 (4,480) 332 (4,600).

*Anal.* Calcd. for  $C_{13}H_{10}N_2O$ : C, 74.2; H, 4.8; N, 13.3. Found: C, 74.00; H, 4.9; N, 13.2.

This compound was also obtained by hydrolysis of **2b** with hydroxide.

2-Amino-5-chloro- $\alpha$ -(2-hydroxyphenyl)benzylamine (**9**).

Zinc dust (50 g.) was added in small portions to a mixture of 12.2 g. (0.05 mole) of **8a**, 100 ml. of ethanol and 100 ml. of concentrated hydrochloric acid. After addition, the mixture was stirred for 2 hours at room temperature. The inorganic material was separated by filtration and the filtrate was made alkaline with aqueous ammonia. It was then partitioned between water and methylene chloride. The methylene chloride layer was washed with water, dried and evaporated. Crystallization of the residue from ether/petroleum ether yielded 5.9 g. (47%) of product with m.p. 88-90°. For analysis it was recrystallized from benzene/petroleum ether; uv:  $\lambda$  max 245  $m\mu$  ( $\epsilon = 9,800$ ) 280 (3,600) sh 296 (2,600); nmr (deuteriochloroform):  $\delta$  4.73 ppm (broad s, 5, NH<sub>2</sub> and OH) 5.2 (s, 1,  $\alpha$ -proton) 6.5-7.4 (m, 7, aromatic H); MS: *m/e* 248 ( $M^+$ ) 230, 214, 196.

*Anal.* Calcd. for  $C_{13}H_{13}ClN_2O$ : C, 62.8; H, 5.2; N, 11.2. Found: C, 62.8; H, 5.1; N, 11.3.

This compound was also formed besides 5-chloro-3-(2-hydroxyphenyl)indazole (**11a**) by reduction of **8a** with lithium aluminum hydride in refluxing tetrahydrofuran.

1,3-Di[4-chloro-2-(3-benzisoxazolyl)phenyl]triazene (**10**).

Sodium nitrite, 3.5 g. (0.05 mole), was added in portions to a stirred solution of 10 g. (0.04 mole) of **8a** in 250 ml. of glacial acetic acid. After stirring for 20 minutes at room temperature, the product had crystallized out. It was collected, washed with water and methanol and was recrystallized from methylene chloride/methanol to yield 6 g. (58.5%) of yellow crystals with m.p. 223-224° dec.; uv:  $\lambda$  max 235  $m\mu$  ( $\epsilon = 38,000$ ) 290 (16,000) 373 (24,500); ir (potassium bromide): 3250  $cm^{-1}$  (NH).

*Anal.* Calcd. for  $C_{26}H_{15}Cl_2N_5O_2$ : C, 62.4; H, 3.0; N, 14.0. Found: C, 62.4; H, 2.9; N, 14.1.

5-Chloro-3-(2-hydroxyphenyl)indazole (**11a**).

A mixture of 5 g. (0.02 mole) of **8a**, 2.5 g. of sodium hydride suspension (50% in mineral oil) and 200 ml. of tetrahydrofuran was heated to reflux overnight under nitrogen atmosphere. The reaction was worked up as described for **11b** (method B) and the product was crystallized from methylene chloride/methanol to yield

3.2 g. (64%) with m.p. 215-217°; uv:  $\lambda$  max 212  $m\mu$  ( $\epsilon = 42,250$ ) infl 229 (23,500) 243 (10,500) sh 275 (4,700) 321 (12,000) infl 334 (8,800); nmr (10% DMSO in deuteriochloroform):  $\delta$  6.9-8.2 ppm (m, 7, aromatic H) 11.0 (s, 1) 12.9 (broad s, 1) (NH and OH); MS: *m/e* 244 ( $M^+$ ), 215, 209, 181, 152.

*Anal.* Calcd. for  $C_{13}H_9ClN_2O$ : C, 63.4; H, 3.8; N, 11.4. Found: C, 64.0; H, 3.6; N, 11.3.

3-(2-Hydroxyphenyl)indazole (**11b**).

A.

Compound **8b**, 1.05 g. (5 mmoles) was added to a suspension of 0.4 g. of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was heated to reflux for 2 hours under an atmosphere of nitrogen. After hydrolysis with 2.5 ml. of water, the inorganic material was separated by filtration. The filtrate was dried and evaporated and the residue was chromatographed over 30 g. of silica gel using methylene chloride. The clean fractions were combined and evaporated. Crystallization of the residue from methylene chloride/hexane yielded 0.42 g. (40%) of colorless crystals with m.p. 157-159°; uv:  $\lambda$  max 213  $m\mu$  ( $\epsilon = 46,000$ ) sh 236 (11,000) 243 (12,100) sh 250 (10,100) 257 (10,050) 274 (6,200) 315 (15,520) sh 325 (12,500); ir (chloroform): 3460  $cm^{-1}$  (OH) 3250 (OH); nmr (10% DMSO in deuteriochloroform): 6.9-8.1 ppm (m, 8, aromatic H) 11.2 (broad s, 1) 12.8 (broad s, 1) (OH and NH); MS: *m/e* 210 ( $M^+$ ) 181, 152.

*Anal.* Calcd. for  $C_{13}H_{10}N_2O$ : C, 74.3; H, 4.8; N, 13.3. Found: C, 74.5; H, 4.7; N, 13.5.

B.

A mixture of 12.6 g. (0.06 mole) of **8b**, 8 g. of sodium hydride suspension (50% in mineral oil) and 400 ml. of tetrahydrofuran was heated to reflux overnight under nitrogen atmosphere. The hydride was destroyed by addition of ethanol and the mixture was partitioned between water and methylene chloride. The organic layer was separated, washed with bicarbonate solution, dried and evaporated. Crystallization of the residue from methylene chloride/hexane yielded 10.1 g. (80%) of product with m.p. 157-159°.

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