

## Ring Closure Reactions with Nitriles. III. Formation of 2-Amino- and 2-Oxo-3-hydroxyindoles from the Reaction of 2'-Aroylacylanilides with Cyanide

Stanley C. Bell and Peter H. L. Wei

Research Division, Wyeth Laboratories, Inc.

Dedicated to Professor Allan R. Day

Treatment of 2'-aroylhaloacylanilides with potassium cyanide produced quinazolines, carbostyrils, and 3-hydroxyindoles. From the reaction of 2'-aroyl-2,2-dichloroacetanilides with cyanide, good yields of 2-amino-3-hydroxyindoles were obtained and their reactions were studied.

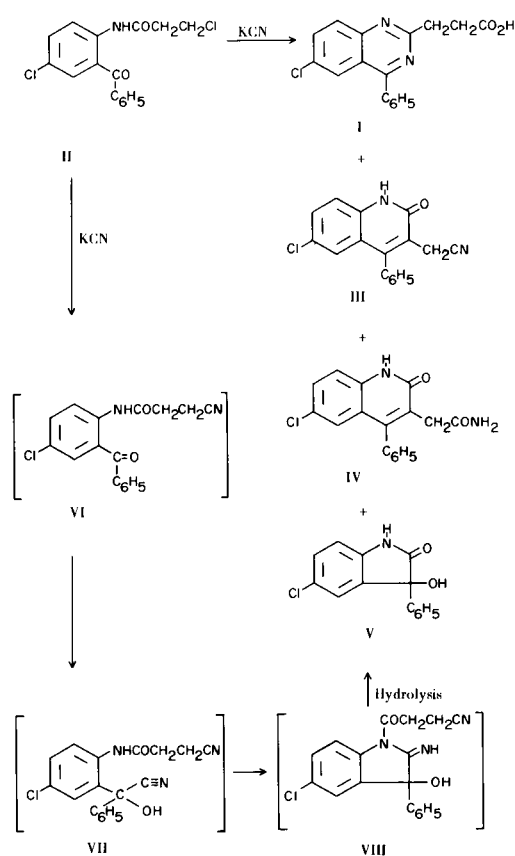
Several cyclization reactions of nitriles that afford fused pyrroles have recently been described (1,2). Some of these reactions, such as the formation of 6-chloro-4-phenyl-2-quinazolinepropionic acid (I) from the reaction of 2'-benzoyl-3,4'-dichloropropionanilide (II) with potassium cyanide, involve several rearrangement steps. In the process of working up the quinazoline-2-propionic acid reaction mixtures, small amounts of several other by-products were isolated. The identification of these by-products indicated that several competitive cyclizations were taking place.

Two of the compounds from the reaction of II with potassium cyanide were 6-chloro-1,2-dihydro-2-oxo-4-phenyl-3-quinolinacetonitrile (III) and its partial hydrolysis product, the 3-quinolineacetamide (IV). Compounds III and IV were identified by comparison of their complex ultraviolet absorption spectra with that of 6-chloro-1,2-dihydro-2-oxo-4-phenylquinoline (3). The occurrence of compounds III and IV was readily explained as arising from a Camps (4) cyclization of the 2-acylaminobenzophenone (II).

A third compound which was isolated was identified as the dioxindole, 5-chloro-3-hydroxy-3-phenyloxindole (V) (5). The unexpected production of this 3-hydroxyindole (V) prompted us to investigate more extensively the reaction of 2'-aroylacylanilides with cyanide, which is the subject of this paper.

The formation of compound V indicated that one mole of potassium cyanide reacted with II to form the intermediate 2'-benzoyl-4'-chloro-3-cyanopropionanilide (VI) (2) and a second mole added to the keto group of VI to form the cyanohydrin (VII). The amide nitrogen atom

of VII, however, did not undergo a cyclization with the nitrile in the 3-position to form the 5-imino-2-pyrrolidinone as previously described (2), but instead reacted with the cyanohydrin nitrile group to form the intermediate



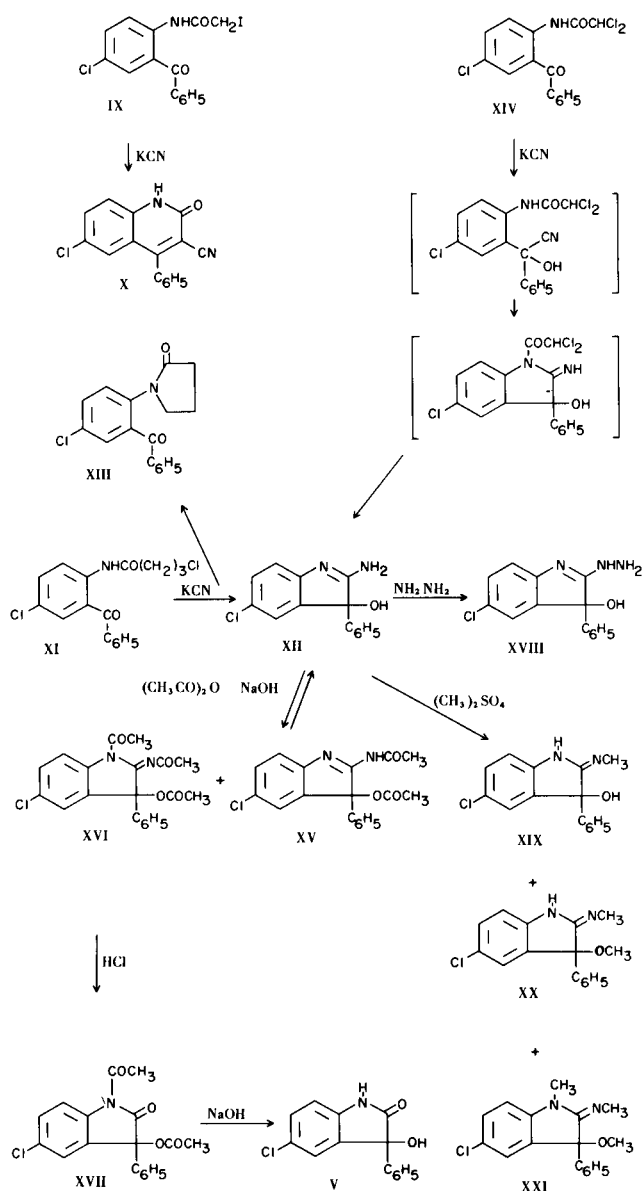
1-(3-cyanopropionyl)-2-imino-3-indolinol (VIII). Hydrolyses of the 1-(2-cyanopropionyl) group and the 2-imino group of compound VIII resulted in the formation of the stable V.

In order to study the scope of the indole formation, several anilides were prepared and reacted with cyanide. 2'-Benzoyl-4'-chloroacetanilide cyclized in the presence of potassium cyanide to form 6-chloro-1,2-dihydro-2-oxo-4-phenylquinoline (3), and 2'-benzoyl-4'-chloro-2-iodoacetanilide (IX) underwent substitution by cyanide and cyclization to form 6-chloro-3-cyano-1,2-dihydro-2-oxo-4-phenylquinoline (X). When either 2-carbethoxyamino-5-chlorobenzophenone or 2-amino-5-chlorobenzophenone was treated with potassium cyanide only unreacted starting material was isolated. The reaction of 2'-benzoyl-4,4'-dichlorobutyranilide (XI) with potassium cyanide, however, did produce 2-amino-5-chloro-3-phenyl-3*H*-indol-3-ol (XII) (6) in low yield, although the major product was 1-(2-benzoyl-4-chlorophenyl)-2-pyrrolidinone (XIII), formed by elimination of hydrochloric acid.

Thus, in order to obtain an optimum yield of a 3-hydroxyindole, it seemed necessary to have an acyl group which would activate the amide proton of the anilide and yet not undergo any of the above side reactions with cyanide. For this purpose, 2'-benzoyl-2,2,4'-trichloroacetanilide (XIV), prepared from 2-amino-5-chlorobenzophenone and dichloroacetyl chloride, was reacted with potassium cyanide. As desired, a good yield of the 3-hydroxyindole (XII) was obtained.

Since 2-amino-3-hydroxyindoles had not been described in the literature (6b), it seemed worthwhile to investigate some of its properties. Treatment of XII with acetic anhydride under various conditions produced the diacetyl and triacetyl derivatives of XII, 2-acetamido-3-acetoxy-5-chloro-3-phenyl-3*H*-indole (XV) and 3-acetoxy-1-acetyl-2-acetylimino-5-chloro-3-phenyl-3-indole (XVI), respectively. Both XV and XVI in base gave back the starting 2-aminoindole (XII). The 2-acetylimino group of XVI hydrolyzed in hydrochloric acid to produce 3-acetoxy-1-acetyl-5-chloro-3-phenyloxindole (XVII) and XVII hydrolyzed further in base to produce the oxindole (V). Treatment of XII with hydrazine caused a displacement of ammonia to afford a 2-hydrazino analog (XVIII).

The reaction of XII with methyl sulfate in alkali produced three methylated derivatives, a mono, a di and a tri-methylated indoline. The location of the methyl groups of these compounds was somewhat difficult to determine and on the basis of their NMR and mass spectra we proposed that the compounds are a 2-methylimino-3-hydroxyindoline (XIX), a 2-methylimino-3-methoxyindoline (XX) and a 1-methyl-2-methylimino-3-methoxyindoline (XXI). Compounds XXI had three methyl singlets ( $\delta$  3.00,  $\delta$  3.11, and  $\delta$  3.24) and the value at the highest



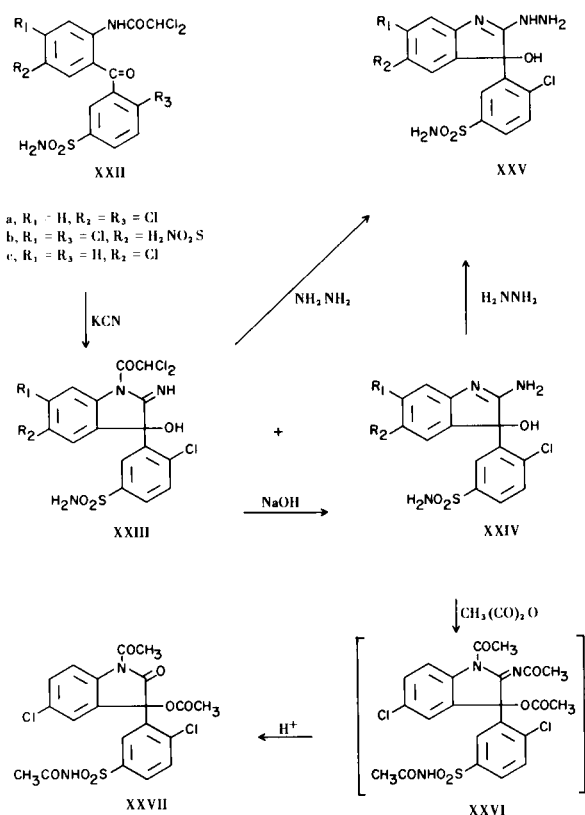
field ( $\epsilon$  3.24) was assigned to the 3-methyl ether. Compound XIX had one three proton singlet at  $\delta$  3.11 which indicated that one of the nitrogen atoms, more likely the nitrogen in the 2 position than the ring nitrogen, was methylated. Although the rate of N-H exchange may be great enough to mask coupling, the absence of any coupling between the *N*-methyl and *N*-H in compounds XIX and XX suggests that they exist in the assigned tautomeric forms. Thus, the two methyl singlets for compound XX at  $\delta$  3.12 and  $\delta$  3.31 were ascribed to the 2-methylimino group and 3-methyl ether group, respectively while the other two singlets of XXI at  $\delta$  3.00 and  $\delta$  3.11 were assigned to the methyl on the ring nitrogen and the 2-methylimino group, respectively. Additional support of the structures was obtained from mass spectral data. In compounds XX and

XXI, the characteristic fragmentation resulting in loss of  $\text{CH}_2\text{O}$  showed the presence of the  $-\text{OCH}_3$  function, whereas this fragmentation was not present in the mono-methylated compound, XIX.

Because of our interest in the pharmacological activity of novel sulfonamide derivatives, we investigated the preparation of 2-amino-3-hydroxyindoles containing sulfamoyl groups on the aromatic rings. When anilides containing a sulfamoyl group in the *meta* position of the benzoyl ring such as 2,2,4'-trichloro-2'-(2-chloro-5-sulfamoylbenzoyl)acetanilide (XXIIa) reacted with potassium cyanide, the proposed intermediate 5-chloro-1-(2,2-dichloroacetyl)-2-imino-3-(2-chloro-5-sulfamoylphenyl)-3-indolinol (XXIIIa) was obtained in addition to 2-amino-5-chloro-3-(2-chloro-5-sulfamoylphenyl)-3H-indol-3-ol (XXIVa). Compound XXIIIa, in turn, was converted to XXIVa by treatment with dilute sodium hydroxide.

Treatment of XXIIIa with hydrazine resulted not only in hydrolysis of the dichloroacetyl group but also in displacement of ammonia to afford XXVa, the 2-hydrazino analog of XXIVa. Similarly, hydrazine reacted with 2-amino-6-chloro-3-(2-chloro-5-sulfamoylphenyl)-5-sulfamoyl-3H-indol-3-ol (XXIVb) to form the corresponding 2-hydrazino analog (XXVb).

When compound XXIVa was heated with a large excess of acetic anhydride, the product that was isolated contained one less nitrogen than the starting material and exhibited



three methyl singlets in the NMR. Apparently a tetra-acetylated intermediate, 3-(5-acetamidobenzoyl-2-chlorophenyl)-3-acetoxy-1-acetyl-2-acetyl-imino-5-chloro-3-indoline (XXVI), had formed, and the 2-acetyl-imino group either hydrolyzed in the reaction mixture or in the work-up to give the triacetylated compound, 3-(5-acetamidobenzoyl-2-chlorophenyl)-3-acetoxy-1-acetyl-5-chloro-oxindole (XXVII).

Additional studies of the reactions of 3-halopropionanilides with cyanide are in progress. We are also continuing the investigation of the products obtained from these reactions and will subsequently report on this work.

## EXPERIMENTAL

Reactions of 2'-Benzoyl-3,4'-dichloropropionanilide (II) with Potassium Cyanide (2).

### Reaction A.

A mixture of 48.3 g. of II, 11.7 g. of potassium cyanide, 300 ml. of dimethoxyethane, and 25 ml. of water was heated to reflux for 9 hours, cooled, and filtered. The precipitate was washed with dimethoxyethane and water and recrystallized from dimethoxyethane to give 5.2 g. of 7-chloro-5-hydroxy-5-phenyl-1,2,3,5-tetrahydropyrrolo[1,2-a]quinazolin-1-one (2), m.p. 236-238°. The filtrate from the reaction mixture, after the addition of an additional 1.5 g. of potassium cyanide, was heated to reflux for an additional 40 hours, filtered to remove insoluble material, and concentrated *in vacuo*. Recrystallization of the residue from benzene gave 5.0 g. of 6-chloro-1,2-dihydro-2-oxo-4-phenyl-3-quinolineacetone (III). A second recrystallization from dimethoxyethane gave pure III, m.p. 273-275°; infrared  $\lambda$  max (potassium bromide) 3.60, 4.49 ( $\text{C}=\text{N}$ ), and 6.10  $\mu$  ( $\text{C}=\text{O}$ ); NMR  $\delta$  3.53 (s,  $\text{CH}_2$ ) and  $\delta$  12.5 (NH); UV  $\lambda$  max (ethanol) 239 ( $\epsilon$ , 40,800), 234 (sh), 279 ( $\epsilon$ , 5,950), 342 ( $\epsilon$ , 6,680), and 355  $\mu$  (sh). The U.V.  $\lambda$  max (ethanol) for 6-chloro-1,2-dihydro-2-oxo-4-phenylquinoline (3) are 237 ( $\epsilon$ , 39,500), 233 (sh), 279 ( $\epsilon$ , 6,200), 340 ( $\epsilon$ , 5,900), and 355  $\mu$  (sh)].

Anal. Calcd. for  $\text{C}_{17}\text{H}_{11}\text{ClN}_2\text{O}$ : C, 69.25; H, 3.76; Cl, 12.04; N, 9.50. Found: C, 69.50; H, 3.75; Cl, 12.18; N, 9.57.

The benzene solution from which III had been obtained was extracted with a sodium carbonate solution. Acidification of the carbonate solution precipitated a small amount (0.2 g.) of 6-chloro-4-phenyl-2-quinazolinepropionic acid (I) (2), m.p. 163-166°.

The benzene solution was washed with water and concentrated to a small volume to precipitate 5-chloro-3-hydroxy-3-phenyl-oxindole (V). Recrystallization from benzene gave 2.0 g. of pure V, m.p. 235-237°; infrared  $\lambda$  max (potassium bromide) 3.00, 3.15 (NH, OH), and 5.84  $\mu$  ( $\text{C}=\text{O}$ ).

Anal. Calcd. for  $\text{C}_{14}\text{H}_{10}\text{ClNO}_2$ (V): C, 64.75; H, 3.88; Cl, 13.66; N, 5.39. Found: C, 65.01; H, 3.84; Cl, 13.50; N, 5.66.

### Reaction B.

A mixture of 29.6 g. of II, 7.2 g. of potassium cyanide, and 360 ml. of 95% ethanol was heated to reflux for 2 hours and filtered while hot. The precipitate was washed with ethanol and water to yield 1.2 g. of 6-chloro-1,2-dihydro-2-oxo-4-phenyl-3-quinolineacetamide (IV), m.p. 315-320° (from dimethylformamide). The NMR spectrum showed a singlet at  $\delta$  3.57 for the  $-\text{CH}_2-$  group; U.V.  $\lambda$  max (ethanol) 239 ( $\epsilon$ , 40,600), 234 (sh), 279 ( $\epsilon$ ,

6.050), 338 ( $\epsilon$ , 7,100), and 352  $m\mu$  (sh).

*Anal.* Calcd. for  $C_{17}H_{13}ClN_2O_2$ (IV): C, 65.20; H, 4.18; Cl, 11.35; N, 8.95. Found: C, 65.29; H, 4.20; Cl, 11.20; N, 8.88.

The above alcoholic solution was concentrated and the residue was washed with cyclohexane. Concentration of the foregoing cyclohexane washes gave 12 g. of ethyl 6-chloro-4-phenyl-2-quinazolinepropionate (2), m.p. 71-73° (from ethanol).

6-Chloro-3-cyano-1,2-dihydro-2-oxo-4-phenylquinoline (X).

A mixture of 12.0 g. of 2'-benzoyl-4'-chloro-2-iodoacetanilide (IX), 150 ml. of ethanol, 6.0 g. of potassium cyanide, and 50 ml. of water was stirred at room temperature for 20 hours. The clear red solution was diluted with 150 ml. of water and chilled to give 5.1 g. of X, m.p. >300° (white solid from dimethylformamide); infrared  $\lambda$  max (potassium bromide) 3.65 (NH), 4.56 (C=N), and 6.07  $\mu$  (C=O).

*Anal.* Calcd. for  $C_{16}H_9ClN_2O$ : C, 68.46; H, 3.23; Cl, 12.63; N, 9.98. Found: C, 68.27; H, 3.27; Cl, 12.70; N, 9.98.

2'-Benzoyl-2,2,4'-trichloroacetanilide (XIV).

To a solution of 2-amino-5-chlorobenzophenone (46 g.) in 200 ml. of chloroform was added, with stirring, a solution of 36 g. of dichloroacetyl chloride in 100 ml. of chloroform. After the evolution of hydrogen chloride had subsided, the solvent was removed *in vacuo* and the residue was recrystallized from ethanol to give 57 g. of product, m.p. 88-90°.

*Anal.* Calcd. for  $C_{15}H_{10}Cl_3NO_2$ : Cl, 31.05; N, 4.09. Found: Cl, 31.30; N, 4.04.

3-(2-Amino-5-chlorobenzoyl)-4-chlorobenzenesulfonamide.

To 180 ml. of chlorosulfonic acid was added, with stirring and cooling, 92.0 g. of 2-amino-2',5'-dichlorobenzophenone. The reaction mixture was heated on the steam bath for 1 hour, cooled, and decomposed on ice. The resultant yellow solid was filtered. The sulfonyl chloride was added to a solution of 350 ml. of ethanol and 250 ml. of concentrated ammonium hydroxide and the mixture was heated on the steam bath for 1.5 hours. The product was cooled, collected, and washed with an alcohol-water mixture to give 58 g. of product, m.p. 213-215°. A sample recrystallized from acetonitrile melted at 216-218°.

*Anal.* Calcd. for  $C_{13}H_{10}Cl_2N_2O_3S$ : C, 45.23; H, 2.92; N, 8.12; Cl, 20.45; S, 9.29. Found: C, 45.36; H, 2.95; N, 8.59; Cl, 20.10; S, 9.00.

The following sulfonamides were prepared according to the above procedure:

3-(2-Amino-5-chlorobenzoyl)benzenesulfonamide.

This compound, m.p. 156-157°, was prepared from 2-amino-5-chlorobenzophenone.

*Anal.* Calcd. for  $C_{13}H_{11}ClN_2O_3S$ : C, 50.25; H, 3.57; N, 9.02. Found: C, 50.11; H, 3.49; N, 8.74.

2-Amino-2',4'-dichloro-5,5'-disulfamoylbenzophenone.

This compound, m.p. 275-276°, was prepared from 2-amino-2',4'-dichlorobenzophenone.

*Anal.* Calcd. for  $C_{13}H_{11}Cl_2N_3O_5S_2$ : C, 36.79; H, 2.61; Cl, 16.71; N, 9.90; S, 15.12. Found: C, 37.13; H, 2.81; Cl, 16.57; N, 10.01; S, 15.22.

2,2,4'-Trichloro-2'-(2-chloro-5-sulfamoylbenzoyl)acetanilide (XXIIa).

A mixture of 20 g. of 3-(2-amino-5-chlorobenzoyl)-4-chlorobenzenesulfonamide, 200 ml. of dioxane, and 10 g. of dichloro-

acetyl chloride was refluxed for 0.25 hour. The reaction mixture was cooled to afford 26 g. of product, m.p. 191-193° (from ethanol).

*Anal.* Calcd. for  $C_{15}H_{10}Cl_4N_2O_4S$ : C, 39.49; H, 2.21; N, 6.14; Cl, 31.05; S, 7.03. Found: C, 39.57; H, 2.21; N, 6.06; Cl, 30.6; S, 7.20.

2,2,4'-Trichloro-2'-(*m*-sulfamoylbenzoyl)acetanilide (XXIIc).

This compound, m.p. 185-186°, was prepared from dichloroacetyl chloride and 3-(2-amino-5-chlorobenzoyl)benzenesulfonamide according to the procedure for XXIIa and was obtained as the ethanol solvate.

*Anal.* Calcd. for  $C_{15}H_{11}Cl_3N_2O_4S \cdot C_2H_6O$ : C, 43.65; H, 3.66; N, 5.98; Cl, 22.74; S, 6.86. Found: C, 43.83; H, 3.56; N, 6.40; Cl, 22.3; S, 7.10.

2,2,5'-Trichloro-2'-(2-chloro-5-sulfamoylbenzoyl)-4'-sulfamoylacetanilide (XXIIb).

This compound, m.p. 264-266°, was prepared from 4-amino-2-chloro-5-(2-chloro-5-sulfamoylbenzoyl)benzenesulfonamide and dichloroacetyl chloride according to the procedure for XXIIa.

*Anal.* Calcd. for  $C_{15}H_{11}Cl_4N_3O_6S_2$ : C, 33.60; H, 2.11; N, 7.85. Found: C, 33.68; H, 1.92; N, 7.87.

2-Amino-5-chloro-3-phenyl-3H-indol-3-ol (XII).

Method A.

To a suspension of 10.0 g. of XIV in 150 ml. of ethanol was added a solution of 6.0 g. of potassium cyanide in 50 ml. of water. The reaction mixture was stirred overnight, filtered from insoluble material, and diluted with water to precipitate 7.0 g. of product. Recrystallization from acetonitrile gave pure XII, m.p. 215-217°.

*Anal.* Calcd. for  $C_{14}H_{11}ClN_2O$ : C, 64.99; H, 4.29; N, 10.83; Cl, 13.71. Found: C, 65.02; H, 3.98; N, 10.70; Cl, 13.70.

Method B.

To a mixture of 13.6 g. of 2-benzoyl-4,4'-dichlorobutyranilide (XI), 1.0 g. of sodium iodide, and 125 ml. of ethanol was added a solution of 4.0 g. of potassium cyanide in 25 ml. of water. The reaction mixture was stirred for 48 hours, diluted with 75 ml. of water, and filtered, separating 5.7 g. of solid. Dilution of the filtrate with more water precipitated 2.2 g. of XII, m.p. 205-207°, which after recrystallization from acetonitrile had a m.p. of 213-214°.

The insoluble compound from the above reaction was 1-(2-benzoyl-4-chlorophenyl)-2-pyrrolidinone (XIII), m.p. 125-127° (from ethanol).

*Anal.* Calcd. for  $C_{17}H_{14}ClNO_2$ : C, 68.12; H, 4.71; Cl, 11.83; N, 4.76. Found: C, 67.98; H, 4.55; Cl, 12.00; N, 4.67.

2-Amino-5-chloro-3-(2-chloro-5-sulfamoylphenyl)-3H-indol-3-ol (XXIVa).

To a suspension of 20 g. of XXIIa in 200 ml. of ethanol was added a solution of 10 g. of potassium cyanide in 50 ml. of water. The reaction mixture was stirred at room temperature for 1 hour and concentrated to dryness, and the residue was dissolved in water. Acidification with acetic acid produced a solid, which was suspended in dilute hydrochloric acid and filtered from insoluble material. Neutralization of the filtrate with sodium carbonate gave 2.3 g. of solid, m.p. 202-212°. Two recrystallizations from alcohol-water gave XXIVa, m.p. 235-236°, as a hemi-hydrate.

*Anal.* Calcd. for  $C_{14}H_{11}Cl_2N_3O_3S \cdot \frac{1}{2}H_2O$ : C, 44.10; H, 3.17; N, 11.02; Cl, 18.60; S, 8.41. Found: C, 44.29; H, 3.04; N, 10.95; Cl, 18.6; S, 8.2; H<sub>2</sub>O, 3.9.

The above insoluble material was recrystallized from ethanol to give 7.3 g. of 5-chloro-1-(2,2-dichloroacetyl)-2-imino-3-(2-chloro-5-sulfamoylphenyl)-3-indolinol (XXIIIa), m.p. 203-205°, as the hemi-ethanolate. The NMR spectrum showed 0.5 mole of ethanol.

*Anal.* Calcd. for  $C_{16}H_{11}Cl_4N_3O_4S \cdot \frac{1}{2}C_2H_6O$ : C, 40.33; H, 2.79; N, 8.30; Cl, 28.02; S, 6.34. Found: C, 39.61; H, 3.03; N, 8.11; Cl, 27.6; S, 6.7.

5-Chloro-3-(*m*-sulfamoylphenyl)-1-(2,2-dichloroacetyl)-2-imino-3-indolinol (XXIIIc).

This compound, m.p. 269-270°, was prepared from XXIIIc and potassium cyanide according to the procedure for XXIIIa and XXIVa.

*Anal.* Calcd. for  $C_{16}H_{12}Cl_3N_3O_4S$ : C, 42.82; H, 2.70; N, 9.36; Cl, 23.71; S, 7.15. Found: C, 42.92; H, 2.58; N, 9.24; Cl, 23.1; S, 7.1.

Also isolated from the reaction was 2-amino-5-chloro-3-(*m*-sulfamoylphenyl)-3*H*-indol-3-ol (XXIVc).

*Anal.* Calcd. for  $C_{14}H_{12}ClN_3O_3S$ : C, 49.78; H, 3.58; N, 12.44; Cl, 10.49; S, 9.49. Found: C, 49.81; H, 3.45; N, 12.61; Cl, 10.6; S, 9.6.

2-Amino-6-chloro-3-(2-chloro-5-sulfamoylphenyl)-5-sulfamoyl-3*H*-indol-3-ol (XXIVb).

This compound, m.p. 248-250°, was prepared from XXIIb and potassium cyanide according to the procedure for XXIVa and was hydrated with 1.5 moles of water.

*Anal.* Calcd. for  $C_{14}H_{12}Cl_2N_4O_5S_2 \cdot 1\frac{1}{2}H_2O$ : C, 35.17; H, 3.16; N, 11.71; Cl, 14.82; S, 13.41;  $H_2O$ , 5.64. Found: C, 34.82; H, 2.75; N, 11.66; Cl, 15.08; S, 13.67;  $H_2O$ , 5.55.

5-Chloro-2-hydrazino-3-(2-chloro-5-sulfamoylphenyl)-3*H*-indol-3-ol (XXVa).

A solution of 2.0 g. of XXIIIa (or XXIVa), 10 ml. of hydrazine hydrate, and 10 ml. of water was heated on the steam bath for 0.5 hour. The reaction mixture was cooled, diluted with water, and acidified with acetic acid. The product was collected, suspended in acetonitrile, and again collected. After recrystallization from alcohol-water there was obtained 1.0 g., m.p. 195-196°.

*Anal.* Calcd. for  $C_{14}H_{12}Cl_2N_4O_3S$ : C, 43.42; H, 3.12; N, 14.47; Cl, 18.31; S, 8.28. Found: C, 43.70; N, 3.51; N, 14.16; Cl, 17.9; S, 8.5.

5-Chloro-2-hydrazino-3-phenyl-3*H*-indol-3-ol (XVIII).

A mixture of 0.5 g. of XII, 5 ml. of hydrazine hydrate, 5 ml. of water, and 20 ml. of ethanol was heated to reflux for 0.5 hour and cooled to yield 0.4 g. of white solid, m.p. 203-204° (from ethanol). The product was solvated with 0.5 mole of ethanol.

*Anal.* Calcd. for  $C_{14}H_{12}ClN_3O \cdot \frac{1}{2}C_2H_6O$ : C, 60.71; H, 5.10; N, 14.16. Found: C, 60.68; H, 4.82; N, 14.31.

6-Chloro-3-(2-chloro-5-sulfamoylphenyl)-2-hydrazino-3-hydroxy-3*H*-indole-5-sulfonamide (XXVb).

A mixture of 0.8 g. of XXIVb, 8 ml. of hydrazine hydrate, and 8 ml. of water was heated to reflux for 0.25 hours. The solution was cooled, diluted with an equal volume of water, filtered from impurities, and acidified with acetic acid. The reaction mixture was chilled overnight, giving 0.7 g. of product, m.p. 212-213° dec.

*Anal.* Calcd. for  $C_{14}H_{13}Cl_2N_5O_5S_2$ : C, 36.06; H, 2.81; N, 15.01; S, 13.75. Found: C, 36.11; H, 2.70; N, 14.60; S, 13.30.

3-Acetoxy-1-acetyl-2-acetylmino-5-chloro-3-phenyl-3-indoline (XVI).

A mixture of 4.0 g. of XII and 50 ml. of acetic anhydride was

refluxed for 1 hour and concentrated to dryness. The residue was recrystallized from ethanol to give 2.5 g. of XVI, m.p. 150-152° infrared  $\lambda$  max (potassium bromide) 5.70 (3-OCOCH), 5.80 (2=N-COCH<sub>3</sub>), and 5.96  $\mu$  (1-COCH). The NMR spectrum showed methyl singlets at  $\delta$  1.43,  $\delta$  2.22, and  $\delta$  3.65, and a doublet for the *ortho* aromatic proton at  $\delta$  8.36 ( $J = 9.0$  cps) (8).

*Anal.* Calcd. for  $C_{20}H_{17}ClN_2O_4$ : C, 62.43; H, 4.45; N, 7.28; Cl, 9.23. Found: C, 62.14; H, 4.16; N, 7.28; Cl, 9.10.

2-Acetamido-3-acetoxy-5-chloro-3-phenyl-3*H*-indole (XV).  
A mixture of 2.0 g. of XII and 30 ml. of acetic anhydride was warmed on the steam bath for 15 minutes and concentrated to dryness. Two recrystallizations from ethanol gave 1.0 g. of XV, m.p. 199-200°; infrared  $\lambda$  max (potassium bromide) 5.70 (3-OCOCH<sub>3</sub>) and 5.84  $\mu$  (2-NCOCH<sub>3</sub>). The NMR spectrum showed methyl singlets at  $\delta$  2.18 and  $\delta$  2.21.

*Anal.* Calcd. for  $C_{18}H_{15}ClN_2O_3$ : C, 63.07; H, 4.41; N, 8.18; Cl, 10.35. Found: C, 62.97; H, 4.35; N, 8.12; Cl, 10.5.

3-Acetoxy-1-acetyl-5-chloro-3-phenyloxindole (XVII).

To a suspension of 2.0 g. of XVI in 20 ml. of ethanol was added 2 ml. of 6*N* hydrochloric acid. The solution was stirred for 45 minutes and the precipitate was filtered to give 0.9 g. of product, m.p. 150-152°; infrared  $\lambda$  max (potassium bromide) 5.60 (3-OCOCH<sub>3</sub> and ring C=O) and 5.80  $\mu$  (1-COCH<sub>3</sub>). The NMR spectrum showed methyl singlets at  $\delta$  2.19 and  $\delta$  2.58 and a doublet for the *ortho* aromatic proton at  $\delta$  8.38 ( $J = 9$  cps).

*Anal.* Calcd. for  $C_{18}H_{14}ClNO_4$ : C, 62.89; H, 4.10; N, 4.08; Cl, 10.31. Found: C, 62.97; H, 4.04; N, 3.90; Cl, 10.20.

To a suspension of 0.8 g. of XVII in ethanol was added a slight excess of sodium hydroxide. After standing for one hour, the mixture yielded 0.3 g. of solid 5-chloro-3-hydroxy-3-phenyloxindole (V).

3-(5-Acetamidosulfonyl-2-chlorophenyl)-3-acetoxy-1-acetyl-5-chlorooxindole (XXVII).

A mixture of 2.0 g. of XXIVa and 50 ml. of acetic anhydride was heated on the steam bath for one hour, evaporated to dryness *in vacuo*, and let stand. Recrystallization of the residue twice from ethanol yielded 1.2 g. of product, m.p. 205-210°, as the hemi-alcoholate; infrared  $\lambda$  max (potassium bromide) 3.15, 5.69, and 5.84  $\mu$ . The NMR spectrum showed methyl singlets at  $\delta$  2.05,  $\delta$  2.30, and  $\delta$  2.67 and an *ortho* aromatic proton doublet at  $\delta$  8.26 ( $J = 9$  cps) (8).

*Anal.* Calcd. for  $C_{20}H_{16}Cl_2N_2O_7S \cdot \frac{1}{2}C_2H_6O$ : C, 48.28; H, 3.67; N, 5.36; Cl, 13.57; S, 6.14. Found: C, 48.53; H, 3.45; N, 5.41; Cl, 13.4; S, 6.10.

5-Chloro-3-methoxy-1-methyl-2-methylimino-3-phenylindoline (XXI).

To a suspension of 2.5 g. of XII in 50 ml. of ethanol and three equivalents of alkali was added dimethyl sulfate until the reaction was no longer basic. The reaction mixture was then made basic with sodium hydroxide and diluted with 10 ml. of water to produce a sticky solid (1.5 g.). Two recrystallizations from an ethanol-water mixture afforded the product, m.p. 109-112°. The NMR spectrum showed methyl singlets at  $\delta$  3.00 (N-CH<sub>3</sub>),  $\delta$  3.11 (=N-CH<sub>3</sub>), and  $\delta$  3.24 (OCH<sub>3</sub>); mass spectrum,  $M^+$  (300).

*Anal.* Calcd. for  $C_{17}H_{17}ClN_2O$ : C, 67.88; H, 5.70; Cl, 11.79; N, 9.32. Found: C, 68.02; H, 5.53; Cl, 11.80; N, 9.55.

To a suspension of 5.0 g. of XII in 100 ml. of ethanol and 1.5 moles of alkali was added dimethyl sulfate until the reaction was neutral. The reaction mixture was made alkaline with sodium hydroxide and diluted with 200 ml. of water. The resultant

hemi-solid was suspended in acetonitrile to afford 1.2 g. of solid, m.p. 175-178°. Recrystallization from acetonitrile produced 0.9 g. of 5-chloro-2-methylimino-3-phenyl-3-indolinol (XIX), m.p. 194-195°. The NMR spectrum showed one methyl singlet at  $\delta$  3.11 (=NCH<sub>3</sub>); mass spectrum, M<sup>+</sup> (276).

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>ClN<sub>2</sub>O: C, 66.06; H, 4.80; Cl, 13.00; N, 10.27. Found: C, 65.80; H, 4.99; Cl, 13.15; N, 10.15.

The acetonitrile solution from which XIX was obtained was concentrated to dryness *in vacuo* to afford 1.1 g. of 5-chloro-3-methoxy-2-methylimino-3-phenylindoline (XX). Recrystallization from an alcohol-water mixture and then from hexane gave pure XX, m.p. 120-122°. The NMR spectrum showed methyl singlets at  $\delta$  3.12 (=NCH<sub>3</sub>) and  $\delta$  3.31 (-OCH<sub>3</sub>); mass spectrum, M<sup>+</sup> (286).

*Anal.* Calcd. for C<sub>16</sub>H<sub>15</sub>ClN<sub>2</sub>O: C, 67.01; H, 5.27; Cl, 12.36; N, 9.77. Found: C, 67.15; H, 5.15; Cl, 12.50; N, 9.78.

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(5a) 3-Substituted-3-hydroxyoxindoles, often referred to as dioxindoles, have been prepared from the reaction of isatins with Grignard reagents; *cf.* M. Kohn and A. Osteretzen, *Monatsh. Chem.*, **31**, 747 (1910); *ibid.*, **32**, 904 (1911); *ibid.*, **37**, 25 (1916); R. C. Elderfield, "Heterocyclic Compounds," Vol. 3, John Wiley and Sons, New York, N. Y. (1952). (b) For comparison, Compound V was prepared from the reaction of 5-chloroisatin and phenyl magnesium bromide.

(6a) Compound XI may also exist as the tautomer, 5-chloro-2-imino-3-phenyl-3-indolinol. (b) A recent publication (R. F. Meyer and M. Zwiesler, *J. Org. Chem.*, **33**, 4274 (1968)) has described the preparation of 3-substituted amino-indol-3-ols from the reaction of 3-hydroxyoxindoles with amines.

(7) The NMR spectra were run in dimethylsulfoxide-d<sub>6</sub> using tetramethylsilane as the internal reference. Infrared spectra were determined in potassium bromide pellets. The authors are indebted to Mr. Bruce Hofmann for assistance in interpreting the infrared spectra and to Dr. Stephen Shrader for mass spectral determinations.

(8) *Cf.* Footnote (4) of Reference 1.

Received March 1, 1969

Radnor, Pennsylvania 19087