Quinazolines. II.[1] Oxidation of 2-Aminoindoles and Related Compounds

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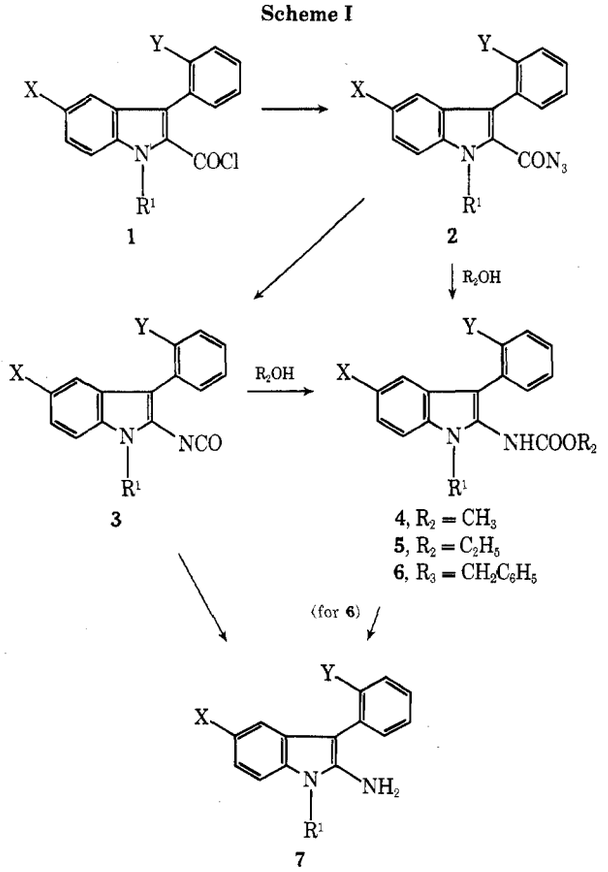
On ozonolysis in acetic acid, 2-amino-5-chloro-1-methyl-3-phenylindole (**7a**) was oxidized to a mixture of 2-imino-3-indolinol (**12a**, 85%) and quinazolinone **11a** (1%), and N-unsubstituted derivative **7c** only to 2-amino-3*H*-indol-3-ol (**14**). Ozonolysis of **7a** in carbon tetrachloride gave only **11a**. Chromic acid oxidation of urethanes **4, 5,** and **6** gave the corresponding allophanates, which were hydrolyzed with base or acid to give quinazolinones **11**. Indole-2-carboxylic acid azides **2a,b**, precursors of **7a,b**, gave **11a,b** (44, 41%) and small amounts of **12a,b** by chromic acid oxidation, while their rearranged isocyanates **3a,b** yielded mainly **12a,b** (47, 64%) together with **11a,b** (4, 6%). Chromic acid oxidation of N-unsubstituted derivative **2c** led to the isolation of the postulated intermediary oxaniloyl azide **27c**. To a crystalline peroxidic product isolated from ozonolysis of **3a**, the 1,2,4-dioxazol-3-one structure **24** is assigned instead of the expected ozonide structure **23**. The Hofmann reaction of 5-chloro-1-methyl-3-phenylindole-2-carboxamide (**28**) with aqueous sodium hypobromite in tetrahydrofuran gave **11**, while similar reaction with aqueous sodium hypochlorite led to a mixture of oxindoles **29** and **30**. By using methanolic sodium hypobromite the expected urethane **4a** was, in addition to the further oxidized product **31**, obtained, although in poor yield. The possible mechanisms involved in these oxidative transformations are discussed.

In our previous study,[1] the synthesis of quinazolinones was accomplished *via* oxidation of indole-1,2-dicarboximides, followed by hydrolysis of their oxidation products. As an extension of this work, we have now investigated the oxidation of 2-aminoindoles and their precursors, *i.e.*, indole-2-carboxylic acid azides and their rearranged isocyanates.

3-Phenylindole-2-carboxylic acid azides **2** were prepared from the corresponding acid chlorides **1**[2] by treatment with sodium azide. Azides **2** slowly rearranged to isocyanates **3** at room temperature over a period of 20–40 days. Urethanes **4, 5,** and **6** were prepared by heating azides **2** or isocyanates **3** in the corresponding alcohols. Hydrogenolysis of benzylurethanes **6a** and **6c** with a palladium on charcoal catalyst[3] afforded 2-aminoindoles **7a** and **7c**, respectively. Compound **7a** was also prepared by hydrolysis of 3a with aqueous potassium hydroxide (Scheme I).

Scheme I



1

2

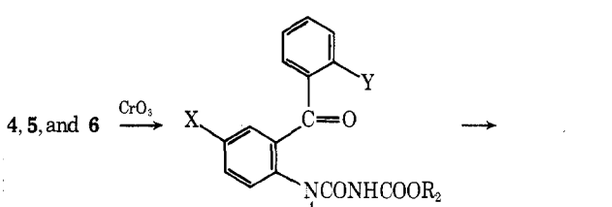
3

4, $R_2 = CH_3$
5, $R_2 = C_2H_5$
6, $R_2 = CH_2C_6H_5$

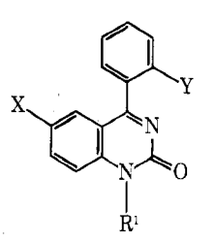
7

a, X = Cl; Y = H; $R_1 = CH_3$
b, X = NO_2; Y = H; $R_1 = CH_3$
c, X = Cl; Y = F; R_1 = H

Oxidation of 2-Aminoindoles 7 and Urethanes 4, 5, and 6.[4] Chromic acid oxidation of urethanes **4, 5,** and **6** gave the expected allophanic acid esters **8, 9,** and **10**, respectively. Although **8a, 9a,** and **10a** could not be isolated in crystalline form, they were hydrolyzed with base or acid to give quinazolinone **11a**[5a,c] in 21–43% yields. In the case of **5c**, the crystalline ethyl allophanate **9c** was isolated, although in poor yield, and shown to be identical with the authentic sample.[1]



8, $R_2 = CH_3$
9, $R_2 = C_2H_5$
10, $R_2 = CH_2C_6H_5$



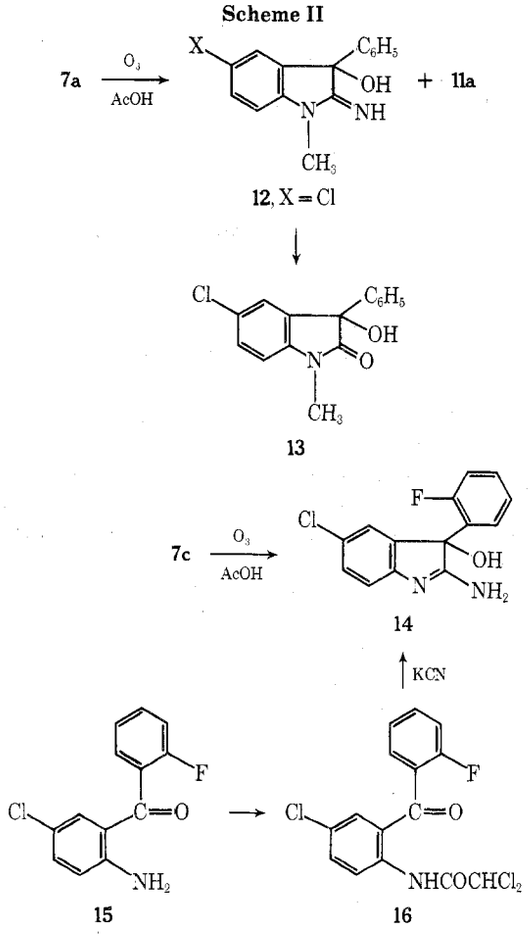
11

a, X = Cl; Y = H; $R_1 = CH_3$
b, X = NO_2; Y = H; $R_1 = CH_3$
c, X = Cl; Y = F; R_1 = H

Chromic acid oxidation of 2-aminoindole **7a** led to a complex mixture with no observable formation of **11a**. On the other hand, ozonolysis of **7a** in acetic acid using ozone–oxygen afforded, in addition to a small amount (1%) of the desired product **11a**, 5-chloro-2-imino-1-methyl-3-phenyl-3-indolinol (**12a**) in 85% yield. Compound **12a** was hydrolyzed with 40% aqueous sodium hydroxide in dimethyl sulfoxide to yield 5-chloro-1-methyl-3-phenyldioxindole (**13**).

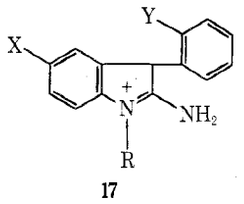
On ozonolysis under the same conditions, **7c** afforded 2-amino-5-chloro-3-(*o*-fluorophenyl)-3*H*-indol-3-ol (**14**), exclusively. The structure of **14** was confirmed by an alternative preparation[6] from the corresponding 2-aminobenzophenone (**15**) as shown in Scheme II.

Scheme II



Ozone rather than oxygen[7] was shown to be the oxidizing agent in the oxidation of **7a** by the fact that no reaction occurred when oxygen was passed into the reaction mixture.

Although no simple explanation for the results observed can be offered at the present time, the formation of **12** and **14** is probably facilitated by the fact that **7** is present in the conjugate acid form **17**[8] in acetic acid. In fact, ozonolysis of

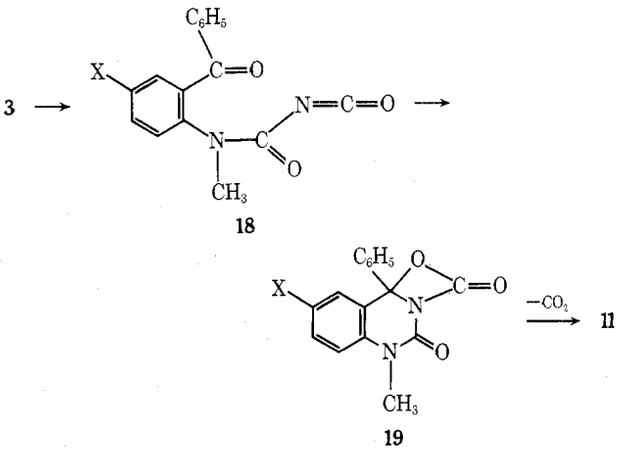


17

7a in the nonpolar solvent carbon tetrachloride[9] gave only **11a** in 7% yield.

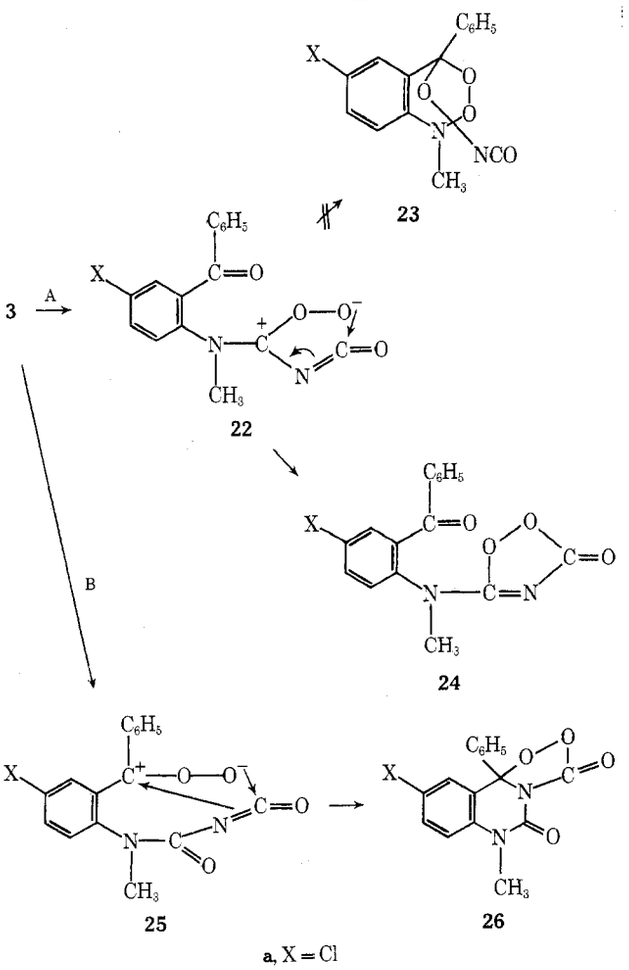
Oxidation of 2-Isocyanatoindoles 3. Chromic acid oxidation of 2-isocyanato-1-methylindoles **3a** and **3b** gave, as the major product, 2-imino-3-indolinols **12a** and **12b**,[10] respectively, together with small amounts of the corresponding **11a** and **11b**, whereas under identical conditions 1-unsubstituted derivative **3c** afforded a complex mixture with no **11c** and **14c** detected.

The formation of **11** as minor products may be explained by initial oxidative cleavage of the indole 2,3 double bond in **3** to give an intermediate **18**. Cyclization of the benzophenone carbonyl group in **18** to the isocyanate group would give an intermediate **19** which eliminates carbon dioxide and yields **11**.[11]



Ozonolysis of **3a** in acetic acid gave, in addition to a small amount of **11a**, a colorless, crystalline peroxidic product of the same molecular formula as that of the expected ozonide **23**. However, this new product did not retain the isocyanate group, as evidenced by the ir spectrum, thus eliminating **23** as a possible structure. On the assumption that this ozonolysis proceeds *via* the formation of either possible zwitterion **22** or **25**,[12] there are possible two other structures, **24** and **26**, which could be formed by the preferential cyclization of **22** and **25** on the isocyanate group rather than on the carbonyl group formed (Scheme III). This

Scheme III



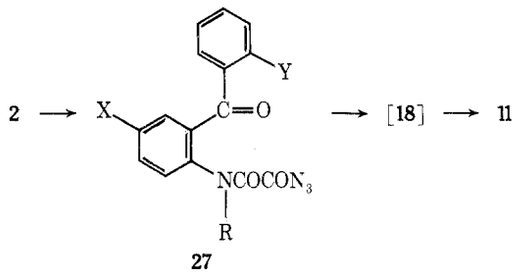
a, X = Cl
b, X = NO_2

might be expected to occur because the isocyanate group should be more reactive as an electrophile. The mass spectrum, which showed major fragment ions characteristic of 2-aminobenzophenones,[13] provided support for structure **24.** Furthermore, the ir absorptions at 1670 (benzophenone C=O), 1638 (C=N), and 1802 cm^{-1} (OCON) seemed more consistent with **24** than with **26.** Thus, we believe structure **24** to be the most likely one for the ozonolysis product of **3.**

Under the same conditions **3b** afforded **24b** as an oil whereas **3c** gave a complicated reaction mixture. Dioxazolones **24a** and **24b** were reduced with sodium iodide to give quinazolinones **11a** and **11b,** respectively.

Oxidation of Indole-2-carboxylic Acid Azides 2. In contrast to isocyanates **3,** chromic acid oxidation of azides **2a** and **2b** gave, as the major product, quinazolinones **11a** and **11b,** respectively, together with small amounts of the corresponding 2-imino-3-indolinols **12a** and **12b.** The latter compounds were probably formed either from isocyanates **3** present as a contaminant in the sample of **2**[14] or those formed by rearrangement prior to oxidation.

The formation of **11** from **2** can be visualized as proceeding *via* a sequence of reactions involving oxaniloyl azides **27** and their rearranged isocyanate intermediates **18.** The



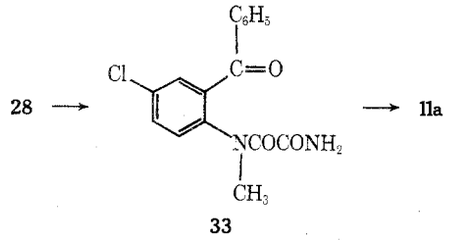
27

a, X = Cl; Y = H; R = CH_3
b, X = NO_2; Y = H; R = CH_3
c, X = Cl; Y = F; R = H

chromic acid oxidation of **2c** led to the isolation of the postulated intermediary oxaniloyl azide **27c.** Compound **27c** is unexpectedly stable and can be kept at room temperature for several weeks without significant change as indicated by the ir spectroscopy. Conversion of **27c** to **11c** was achieved by refluxing in toluene for 6 hr.

Hofmann Reaction of Indole-2-carboxamide 28. Finally, we examined the applicability of the Hofmann reaction[15] to the preparation of 2-aminoindoles **2.** Although 2-aminoindoles have been prepared by other several methods[7] in addition to the Curtius reaction of indole-2-carboxylic acid azides, no reports have appeared on a Hofmann reaction of indole-2-carboxamide.

When a solution of indole-2-carboxamide **28** in tetrahydrofuran[16] was treated with aqueous sodium hypobromite, the unexpected quinazolinone **11a** was obtained in 16% yield together with an unknown dimeric product.[17] The



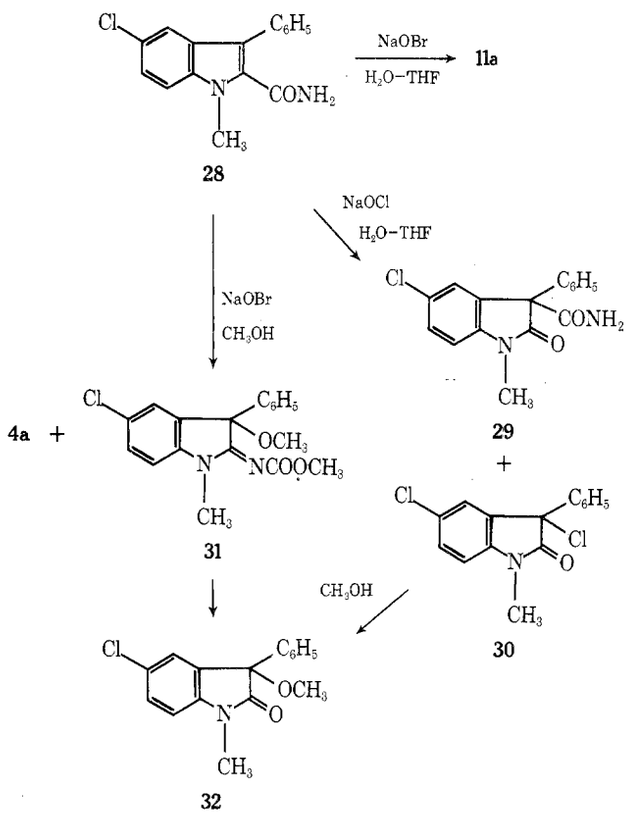
33

reaction probably proceeds *via* initial rearrangement to 2-isocyanato- or 2-aminoindoles **3a** or **7a,** followed by oxidation of the indole 2,3 double bond by the hypobromite present to give **11a.** In fact, both **3a** and **7a** on treatment with aqueous potassium hypobromite gave **11a** in yields of 15 and 17%, respectively.

An alternative route to **11a** involves initial oxidation to an oxamide such as **33,** followed by rearrangement and subsequent cyclization to give **11a.** The inertness of a solution of methyl 5-chloro-1-methyl-3-phenylindole-2-carboxylate (**34**) in tetrahydrofuran toward sodium hypobromite, however, seems to exclude this possibility, although oxamide **33** has been successfully converted to **11a** by performing the Hofmann reaction, as reported in a subsequent paper.[18]

The use of 2.5 molar equiv of aqueous sodium hypochlorite with the addition of tetrahydrofuran led to the formation of oxindoles **29**[19] (34%) and **30** (16%) (Scheme IV) as

Scheme IV



the major products. The structures of these compounds were assigned on the basis of their spectroscopic data. Compound **29** was shown to be identical with the sample obtained as a by-product from chromic acid oxidation of **28** and hydrolyzed to 5-chloro-1-methyl-3-phenyloxindole.[20]

The expected urethane **4a** was obtained, although in poor yield (2%), by employing the Jeffreys modification[15] of the Hofmann reaction. The major product was the further oxidized product **31** (27%), which was easily hydrolyzed to 3-methoxy-3-phenyloxindole(**32**) with acid. The structure of **32** was confirmed by an alternate preparation from **30** by heating with methanol.[21]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (Nujol mulls) were measured on a Hitachi Model EPI-G3 spectrophotometer and nmr spectra on a Varian T-60 instrument using tetramethylsilane as an internal standard. Mass spectra were taken on a Shimadzu LKB instrument with the direct sample inlet system and ionizing potential at 70 eV. Ozone was generated from oxygen using a Nippon ozone 0-10-2 ozonator. All solutions were

Table I

Compd[a]	Method	Recrystn solvent	Mp, °C	Yield, %
2b	A		174–175 dec	95.3
2c[b]	A		113–116 dec	96.7
3b	A		>300	Quantitative
3c	A		77–82	Quantitative
5c	C	EtOH	130.5–132	92.4
6a	B	EtOH	163.5–164.5	39.6
6c	B	*i*-PrOH	115.5–116.5	80.6
7c HCl	D	EtOH	239–241.5	79.8
12b	H	EtOH	227.5–229	46.8[c]

[a] Satisfactory analytical data (±0.4% for C, H, Cl, and N) were reported for all new compounds except **2c** listed in the table: Ed. [b] A satisfactory carbon analysis could not be obtained. [c] Quinazolinone **11b** was obtained in 3.7% yield as the minor product.

dried over anhydrous sodium sulfate and solvents were evaporated under water-aspirator pressure.

The following experiments are typical and illustrate the preparation of the remaining compounds listed in Table I.

5-Chloro-1-methyl-3-phenylindole-2-carboxylic Acid Azide (2a) and Its Conversion into 5-Chloro-2-isocyanato-1-methyl-3-phenylindole (3a). Method A. A mixture of 28.6 g of 5-chloro-1-methyl-3-phenylindole-2-carboxylic acid and 100 g of thionyl chloride was heated under reflux for 1 hr. Excess thionyl chloride was evaporated under reduced pressure and the residual acid chloride was dissolved in 250 ml of acetone. To the cooled solution was added in one portion a solution of 10 g of sodium azide in 30 ml of water. The temperature rose from 5 to 25°. The reaction mixture was cooled to 10° and stirred for 30 min, and 250 ml of water was added. The precipitate that formed was collected by filtration, washed with water followed by 50% aqueous acetone, and dried in a vacuum desiccator at 10° to give 30 g (96.4%) of **2a**: mp 91–94° dec; ir 2130 (N_3), 1666 cm^{-1} (CO). The azide **2a** was too unstable for analysis.

On standing at room temperature, the azide **2a** slowly rearranged to isocyanate **3a**. The course of the reaction was monitored by infrared spectroscopy. After 2 weeks, one-half of **2a** remained. Conversion to **3a** was complete in 40 days: mp 153° dec; ir 2260 cm^{-1} (NCO).

Anal. Calcd for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; Cl, 12.54; N, 9.91. Found: C, 68.09; H, 3.92; Cl, 12.70; N, 10.00.

Methyl 5-Chloro-1-methyl-3-phenylindole-2-carbamate (4a). Method B. A mixture of 1.5 g of **3a** and 50 ml of methanol was heated under reflux for 1 hr. An insoluble material was filtered off and the filtrate was concentrated to about 20 ml and cooled. The precipitate was collected by filtration to give 1.0 g (59.9%) of **4a** as colorless needles: mp 143–145°; ir 3175 (NH), 1722, 1698 cm^{-1}; nmr ($CDCl_3$) δ 3.56 (s, 3, CH_3), 3.71 (s, 3, CH_3), 6.54 (s, 1, D_2O exchangeable, NH), 7.16–7.70 (m, 8, aromatic H).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.26; N, 8.90. Found: C, 65.03; H, 4.74; Cl, 11.22; N, 8.88.

Ethyl 5-Chloro-1-methyl-3-phenylindole-2-carbamate (5a). Method C. A mixture of 5.8 g of **2a** and 300 ml of ethanol was refluxed for 2 hr. After evaporation of ethanol, the residue was recrystallized from isopropyl alcohol to give 5.3 g (86.4%) of **5a**, mp 122–123.5°. Further recrystallization from isopropyl alcohol afforded colorless prisms: mp 123–124°; ir 3220, 3130, 1712 cm^{-1}.

Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; Cl, 10.78; N, 8.52. Found: C, 66.03; H, 5.03; Cl, 10.96; N, 8.50.

2-Amino-5-chloro-1-methyl-3-phenylindole (7a). Method D. From 6a. The procedure was essentially that used for the preparation of 2-aminoindole by Rinderknecht, *et al.*[3] A solution of 2.8 g of **6a** in 70 ml of ethanol containing 1 ml of concentrated hydrochloric acid was hydrogenated over 1.0 g of 5% palladium on charcoal until hydrogen uptake had ceased. The catalyst was removed and the filtrate was evaporated. The residue was recrystallized from a mixture of ethanol and ether to give 1.53 g of the hydrochloride of **7a**, mp 254–259° dec. The filtrate was evaporated to dryness and the residue was recrystallized from a mixture of ethanol and acetone to yield an additional 0.43 g of product, mp 257–260° dec, for a combined yield of 1.96 g (93.3%): ir 1700 (C=N), 1610 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}Cl_2N_2$: c, 61.45; H, 4.81; Cl, 24.18; N, 9.55. Found: C, 61.83; H, 4.77; Cl, 24.13; N, 9.46.

The hydrochloride (0.41 g) was suspended in ether and neutralized with aqueous ammonia. The ether layer was separated, washed with water, dried, and evaporated to give 0.31 g (86.3%) of the free base of **7a**, mp 128–131.5°. Two recrystallizations from a mixture of ether and pentane afforded colorless prisms: mp 133–136°; ir 3477, 3377 cm^{-1}; nmr (CCl_4)[9] δ 2.90 (s, NCH_3 in the imino tautomer), 3.35 (s, NCH_3 in the amino tautomer), 3.86 (broad s, 2, D_2O exchangeable, NH_2), 6.87–7.35 (m, 7, aromatic H).

Method E. From 3a. A mixture of 5.0 g of **3a**, 30 ml of benzene, and 20 ml of 50% potassium hydroxide solution was stirred and heated under reflux for 5 min. After cooling, the benzene layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with water, dried, and evaporated. The residue was triturated with ether to give 3.5 g (77.1%) of **7a**, mp 131–135°.[22]

Ethyl 4-[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]allophanate (9c). Method F. To a suspension of 1.0 g of **5c** in 10 ml of acetic acid was added a solution of 1.0 g of chromic anhydride in 1 ml of water. After stirring at room temperature for 15 hr, the reaction mixture was made basic with aqueous ammonia and extracted with chloroform. The chloroform extracts were combined, washed with water, dried, and evaporated. The oily residue was crystallized from ethanol with activated carbon to give 0.28 g of crude **9c**, mp 162–180°. Three recrystallizations from ethanol afforded slightly yellow needles, mp 207–207.5°.[1,22]

Base Hydrolysis of Ethyl 4-(4-Chloro-2-benzoylphenyl)-4-methylallophanate (9a). Following the procedure described in method F, there was obtained 1.92 g of crude **9a** as an oil from 2.0 g of **5a**. The crude **9a** was dissolved in 20 ml of ethanol, mixed with 5 ml of 20% sodium hydroxide solution, and heated under reflux for 30 min. After evaporation of ethanol, the precipitate was collected by filtration, washed with water, and recrystallized from isopropyl alcohol to give 0.60 g (36.4% from **5a**) of **11a**, mp 218–221°.[5c,22]

Acid Hydrolysis of Benzyl 4-(4-Chloro-2-benzoylphenyl)-4-methylallophanate (10a). The crude **10a** (0.94 g from 1.0 g of **6a**) was dissolved in 9 ml of ethanol, mixed with 3 ml of concentrated hydrochloric acid, and heated under reflux for 1 hr. After evaporation of ethanol, the residue was made basic with aqueous ammonia and the precipitate was collected by filtration and washed with water. Recrystallization from ethanol afforded 0.30 g (43.3% from **6a**) of **11a**, mp 218–221°.[22]

The crude **8a** (1.0 g from 1.0 g of **4a**) was hydrolyzed in the same way to yield 0.18 g (21.2% from **4a**) of **11a**, mp 215–218°.[22]

5-Chloro-2-imino-1-methyl-3-phenyl-3-indolinol (12a). Method G. From 7a. An ozone–oxygen stream was passed through a stirred solution of 0.50 g of **7a** in 10 ml of acetic acid at 10–15° for 10 min. The ozonized solution was diluted with 50 ml of water and extracted with chloroform. The chloroform extracts were combined, washed with water, dried, and evaporated. Trituration of the residue with ether followed by recrystallization from isopropyl alcohol furnished 7 mg (1.3%) of **11a**, mp 220.5–224°.[22]

The aqueous layer that separated from the chloroform layer was made basic with aqueous ammonia and extracted with chloroform. The organic extracts were combined, washed with water, dried, and evaporated. Recrystallization of the residue from isopropyl alcohol afforded 0.45 g (84.7%) of **12a** as off-white prisms: mp 200–200.5°; ir 3275 (NH), 3110 (OH), 1648 (C=N), 1610, 1600 cm^{-1}; mass spectrum *m/e* 272 (M^+, base peak).

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; Cl, 13.00; N, 10.27. Found: C, 66.10; H, 4.61; Cl, 13.28; N, 10,08.

Method H. From 3a. To a suspension of 1.0 g of **3a** in 10 ml of acetic acid was added a solution of 1.0 g of chromic anhydride in 1 ml of water at 15–20°, and the mixture was stirred at room temperature for 3 hr. It was then diluted with water and extracted with chloroform. The insoluble material that formed in the course of extraction was collected by filtration to give 0.94 g of crystals, the infrared spectrum of which [3350–2700, 1700 (C=N), 1615, 935 cm^{-1} (CrO_4^{2-})] indicated that it was probably a chromic acid salt of **12a**. The free base was liberated with aqueous ammonia and recrystallized from isopropyl alcohol to give 0.62 g (64.3%) of **12a** as off-white prisms, mp 199.5–200°.[22]

The chloroform extracts were combined, washed with water, dried, and evaporated. The residue was triturated with ether and recrystallized from isopropyl alcohol to give 0.06 g (6.3%) of **11a**, mp 222–223°.[22]

5-Chloro-1-methyl-3-phenyldioxindole (13). To a solution of 50 mg of **12a** in 4 ml of dimethyl sulfoxide was added 2 ml of 40% sodium hydroxide solution, and the mixture was stirred and heat-

ed to 140° for 1 hr. After cooling, the reaction mixture was diluted with water, acidified with hdyrochloric acid, and extracted with ether. The ether extracts were combined, washed with water, dried, and evaporated. The residue was triturated with isopropyl ether and filtered to give 5 mg (10%) of **13**,[20,22] mp 169–171°. Recrystallization from ether afforded colorless prisms: mp 172–173°; ir 3305, 1717 cm^{-1}.

2-Amino-5-chloro-3-(*o*-fluorophenyl)-3*H*-indol-3-ol (14). Method I. From 7c. A suspension of 1.0 g of **7c** HCl in 10 ml of ether was made basic with aqueous ammonia. The ether layer was separated, washed with water, dried, and evaporated to give 0.88 g of the free base of **7c** as a colorless oil. The base **7c** (0.50 g) was dissolved in 14 ml of acetic acid and subjected to a stream of ozone–oxygen at 14° for 1 hr. The ozonized solution was diluted with water, made basic with 10% sodium hydroxide solution, and extracted with ether. The ether extracts were combined, washed with water, dried, and evaporated. The residue was crystallized from a mixture of ether and isopropyl ether to give 0.12 g (22.6%) of **14**, mp 205.5–207.0°. Recrystallization from isopropyl alcohol furnished colorless needles: mp 205.5–206.5°; ir 3475, 3315, 1650 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClFN_2O$: C, 60.77; H, 3.64; Cl, 12.81; N, 10.12. Found: C, 60.53; H, 3.50; Cl, 12.60; N, 10.00.

Method J. From 2-Amino-5′-chloro-2′-fluorobenzophenone (15).[23] To a solution of 2.3 g of **15** in 10 ml of chloroform was added a solution of 1.8 g of dichloroacetyl chloride in 5 ml of chloroform at 5–10°, and the mixture was stirred at room temperature for 3.5 hr. After evaporation of the solvent, the residue was crystallized and recrystallized from ethanol to give 2.05 g (61.7%) of **2′-(*o*-fluorobenzoyl)-2,2,4′-trichloroacetanilide (16)** as yellow needles, mp 90–99.5°.

Anal. Calcd for $C_{15}H_9Cl_3FNO_2$: C, 49.96; H, 2.52; Cl, 29.49; N, 3.88. Found: C, 50.03; H, 2.53; Cl, 29.28; N, 3.87.

To a solution of 1.5 g of **16** in 22 ml of ethanol was added a solution of 0.89 g of potassium cyanide in 7 ml of water. The reaction mixture was stirred at room temperature for 4 hr and diluted with water. The precipitate was collected by filtration and recrystallized from isopropyl alcohol to give 0.45 g (39.1%) of **14**, mp 205.5–206.5°.[22]

Ozonolysis of 7a in Carbon Tetrachloride. An ozone–oxygen stream was passed through a stirred suspension of 1.0 g of **7a** in 30 ml of carbon tetrachloride at −5° for 30 min. During the reaction, an orange-red solution formed from the colorless suspension and then a new suspension appeared. The precipitate was collected by filtration, dissolved in chloroform, and mixed with 5 g of silica gel. After evaporation of the solvent, the residue was placed on a column of 30 g of silica gel. Elution with ethyl acetate and recrystallization from isopropyl alcohol gave 0.07 g (6.6%) of **11a**, mp 221–223°.[22]

5-(2-Benzoyl-4-chloro-*N*-methylanilino)-1,2,4-dioxazol-3-one (24a). An ozone–oxygen stream was passed through a stirred suspension of 2.0 g of **3a** in 30 ml of acetic acid at 15° for 1 hr. The resulting solution was diluted with water and extracted with ether. The extracts were combined, washed with dilute sodium hydroxide solution and then with water, dried, and evaporated. The residue was triturated with ether and filtered to give 1.1 g (47.0%) of crude **24a**, mp 102–103° dec. The crude product was dissolved in tetrahydrofuran and ether was added. The precipitate that immediately formed was filtered off, the filtrate was evaporated to dryness, and the residue was again dissolved in tetrahydrofuran. This process was repeated three times to remove a small amount of contaminating **11a**. Recrystallization of the residue from a mixture of tetrahydrofuran and ether afforded 0.47 g of colorless needles. The product was shown to be pure **24a** by tlc: mp 103.5–105.5 dec; ir 1802 (OCON), 1670 (benzophenone C=O), 1638 (strong, C=N), 1596 cm^{-1}; nmr ($CDCl_3$) δ 3.43 (s, 3, NCH_3), 7.30–7.90 (m, 8, aromatic H): mass spectrum *m/e* (rel intensity) 286 (1), 269 (3), 242 (34), 228 (3), 214 (3), 105 (7), 77 (12), 44 (100).

Anal. Calcd for $C_{16}H_{11}ClN_2O_4$: C, 58.11; H, 3.35; Cl, 10.72; N, 8.47. Found: C, 58.29; H, 3.25; Cl, 10.82; N, 8.57.

The above pure sample (60 mg), when kept at room temperature for 1 month, decomposed to give a brown solid, which after recrystallization from isopropyl alcohol yielded 12 mg (24.4%) of **11a**, mp 218–221.5°.[22]

There was obtained a total of 0.10 g (5.2%) of **11a** from both the original ether filtrate and the insoluble compounds at purification.

The crude oil dioxazolone **24b** was obtained from similar ozonolysis of **3b** in 53.3% yield together with a 5.2% yield of **11b**.

Reduction of 24a with Sodium Iodide. To a cold suspension of 0.20 g of **24a** in 6 ml of acetic acid was added in one portion a solution of 0.18 g of sodium iodide in 4.5 ml of acetic acid. Immediate iodine formation occurred. After stirring for 5 min, the precipitate formed was collected by filtration, washed successively with water, aqueous ammonia and ether, and recrystallized from ethanol to give 45 mg of **11a**, mp 223–224°.[22] The acetic acid filtrate was diluted with water. Filtration of the resulting precipitate and recrystallization from ethanol gave an additional 45 mg of **11a** for a combined yield of 90 mg (57.5%).

A similar reduction of the crude dioxazolone **24b** gave **11b**[5b,22] in 65.7% yield.

Chromic Acid Oxidation of 2a. Compound **2a**, prepared from 2.0 g of the corresponding indole-2-carboxylic acid in the same way as in method A immediately before use, was suspended in 20 ml of acetic acid and treated with a solution of 2.0 g of chromic anhydride in 2 ml of water. The mixture was stirred at room temperature for 3 hr and diluted with water. The precipitate was collected by filtration, washed with water and aqueous ammonia, and dried to give 1.2 g of crude **11a**, mp 200–202° dec. The filtrate was made basic with aqueous ammonia. The precipitate was collected by filtration, washed with dilute hydrochloric acid, and dried to give an additional 0.09 g of **11a**. The two crops were combined and chromatographed over 30 g of silica gel with ethyl acetate. Evaporation of the combined pure fractions and recrystallization from isopropyl alcohol afforded 0.84 g (44.2% from the indole-2-carboxylic acid) of **11a**, mp 223.5–224.5°.[22] A small amount of **12a** was present in the hydrochloric acid washings as determined by thin layer chromatography.

In another run, the compound **12a**[22] was isolated in 4.5% yield together with a 32.9% yield of **11a**.

A similar oxidation of **2b** gave **11b** and **12b**[22] in 40.8 and 16.5% overall yields from the indole-2-carboxylic acid.

4′-Chloro-2′-(*o*-fluorobenzoyl)oxaniloyl Azide (27c). To a suspension of 1.0 g of **2c** in 10 ml of acetic acid was added a solution of 1.0 g of chromic anhydride in 1 ml of water, and the mixture was stirred at room temperature for 3 hr. The precipitate that formed was collected by filtration, washed with water, and dried to give 0.14 g (12.7%) of **27c**: mp 105–106° dec; ir 3230 (NH), 2230, 2165 (N_3), 1720, 1700 (COCO), 1640 (benzophenone CO), 1615 cm^{-1}.

Anal. Calcd for $C_{15}H_8ClFN_4O_3$: C, 51.97; H, 2.33; Cl, 10.23; N, 16.16. Found: C, 52.07; H, 2.29; Cl, 10.38; N, 15.91.

Conversion of 27c to 11c. A suspension of 0.10 g of **27c** in 3 ml of toluene was stirred and heated under reflux for 6 hr. After cooling, the precipitate was collected by filtration and washed with ether to give 55 mg (69.6%) of **11c**, mp >300°.[1,22]

Reaction of 5-Chloro-1-methyl-3-phenylindole-2-carboxamide (28)[2c] with Sodium Hypobromite. Method K. In Water–Tetrahydrofuran. Bromine (1.92 g, 12 mmol) was added dropwise to a solution of 2.4 g (60 mmol) of sodium hydroxide in 20 ml of water cooled to 0°. To the clear yellow solution was added immediately a solution of 1.0 g (3.5 mmol) of **28** in 20 ml of tetrahydrofuran, and the mixture was stirred and heated under reflux for 5 hr. After cooling, the organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with saturated brine, dried, and evaporated. The residue was chromatographed over 100 g of silica gel with ethyl acetate, followed by ethyl acetate–ethanol (9:1, v/v). Evaporation of the pure fractions eluted with ethyl acetate yielded 0.15 g (15.8%) of **11a**, mp 223–223.5°.[22]

The fractions eluted with ethyl acetate–ethanol (9:1) left 0.27 g of unidentified dimeric product as an amorphous solid: ir 1665 cm^{-1} (amide CO?); nmr (CCl_4) δ 3.20 (s, 3, NCH_3), 3.88 (s, 3, NCH_3), 6.47–7.55 (m, 18, aromatic H); mass spectrum *m/e* (M^+), 494 ($M - CONH_2$?), 284, 270, 256, 221.

Anal. Calcd for $C_{31}H_{24}Cl_2N_4O$: C, 69.02; H, 4.48; Cl, 13.14; N, 10.38. Found: C, 67.64; H, 4.53; Cl, 13.00; N, 11.94.

The dimer was recovered unchanged both from base hydrolysis in aqueous ethanol and dimethyl sulfoxide, and from chromic acid oxidation in acetic acid.

Method L. In Methanol. Compound **28** (1.43 g, 5 mmol) was added to a solution of 0.92 g (40 mmol) of sodium in 55 ml of methanol. To the suspension was added with stirring 3.2 g (20 mmol) of bromine, and the mixture was stirred and refluxed for 35 min. After evaporation of the solvent, the residue was washed with water, dissolved in chloroform, and chromatographed over 100 g of silica gel with chloroform. The first eluted product, 30 mg (1.9%), mp 139–141°, was found to be urethane **4a**.[22] The second product which was eluted was recrystallized from methanol to give 0.46 g (26.7%) of **5-chloro-3-methoxy-2-methoxycarbonylimino-1-methyl-3-phenylindoline (31)**, mp 173–174.5°. Further recrystal-

lization afforded colorless pillars: mp 174–175°; ir 1722, 1693, 1612 cm^{-1}; nmr ($COCl_3$) δ 3.25 (s, 3, CH_3), 3.33 (s, 3, CH_3), 3.45 (s, 3, CH_3), 6.80–7.43 (m, 8, aromatic H); mass spectrum *m/e* 344 (M^+).

Anal. Calcd for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; Cl, 10.28; N, 8.12. Found: C, 62.71; H, 4.93; Cl, 10.24; N, 8.19.

Repetition of the same reaction using 0.23 g of sodium and 0.8 g of bromine led to a 33% recovery of unreacted **28** in addition to a small amount of **4a** and a 13% yield of **31**.

5-Chloro-1-methyl-3-phenyloxindole-3-carboxamide (29) and 3,5-Dichloro-3-phenyloxindole (30). A 1.8 *N* solution of sodium hypochlorite was prepared by the procedure described by Mallory.[24] To 5 ml (9 mmol) of the sodium hypochlorite solution which had been cooled to −10° was added in one portion a cold solution of 1.0 g (3.5 mmol) of **28** in 20 ml of tetrahydrofuran. The mixture was stirred at −10 to −7° for 1 hr and at room temperature for 1 hr. The tetrahydrofuran layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with saturated brine, and evaporated. The residue was crystallized from chloroform to yield 0.22 g of **29**, mp 209.5–212°. Two recrystallizations from ethanol afforded colorless prisms:[20,22] mp 210–214°; ir 3390, 3235, 1705 (CO), 1676 (amide CO), 1610 cm^{-1}; nmr (DMSO-d_6) δ 3.24 (s, 3, CH_3), 7.10–7.72 (m, 10, aromatic H and NH_2).

Anal. Calcd for $C_{16}H_{13}ClN_2O_2$; c, 63.90; H, 4.36; Cl, 11.79; N, 9.31. Found: C, 64.24; H, 4.39; Cl, 12.00; N, 9.11.

The chloroform filtrate was chromatographed over 50 g of silica gel with chloroform, followed by chloroform–ethanol (9:1, v/v). The oil eluted first with chloroform was crystallized and recrystallized from isopropyl alcohol to give 0.16 g (15.6%) of **30** as colorless prisms: mp 103–105°; ir 1737, 1612 cm^{-1}; mass spectrum *m/e* 291 (M^+), containing two chlorine atoms.

Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.67; H, 3.80; Cl, 24.27; N, 4.79. Found: C, 61.53; H, 3.88; Cl, 23.91; N, 4.71.

Continued elution with chloroform separated a second fraction which on trituration with ether gave a trace amount of **11a**.[22] The third fraction eluted with chloroform–ethanol (9:1) left 0.18 g of an oil which was crystallized from isopropyl alcohol to yield an additional 0.14 g of **29**, mp 210.5–212°, for a combined yield of 0.36 g (34.1%).

When the same reaction was repeated using 10 ml (18 mmol) of the sodium hypochlorite solution, there were obtained only **30** (46.3%) and **11** (2.9%) with no **29** detected.

5-Chloro-3-methoxy-3-phenyloxindole (32). Method M. From 31. A mixture of 100 mg of **31**, 3 ml of ethanol, and 1 ml of 20% hydrochloric acid was stirred and heated under reflux for 30 min. The reaction mixture was concentrated and the residue was partitioned between water and ether. The aqueous layer was washed with ether. The combined ether extracts were washed with water, dried, and evaporated. The residue was triturated with ether to give 70 mg (76.6%) of **32**, mp 120–125°. Recrystallization from ether afforded colorless prisms: mp 128–132°; ir 1735, 1615 cm^{-1}; nmr (CCl_4) δ 3.10 (s, 3, CH_3), 3.16 (s, 3, CH_3), 6.68–7.55 (m, 8, aromatic H).

Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; Cl, 12.32; N, 4.87. Found: C, 66.43; H, 4.73; Cl, 12.33; N, 5.02.

Method N. From 30. A solution of 0.20 g of **30** in 5 ml of methanol was heated under reflux for 2 hr. The solvent was evaporated and the residue was crystallized from isopropyl ether to yield 0.17 g (86.3%) of **32**, mp 127–130°.[22]

Reaction of 3a with Potassium Hypobromite. Method O. Bromine (1.0 g) was added to a solution of 1.7 g of potassium hydroxide in 10 ml of water cooled to 0°. To the clear yellow solution was added 1.42 g of **3a**. The mixture was stirred at 0° for 30 min and at room temperature for 1 hr, and then heated to 70–80° for 1 hr. After cooling the gummy solid that formed was separated by decantation, washed with water, and dissolved in ethanol by heating. The insoluble material was filtered off and discarded. The filtrate was concentrated to dryness, dissolved in chloroform, and chromatographed over 50 g of silica gel. Elution with ethyl acetate separated an oily solid which on trituration with ether gave 0.24 g (17.3%) of **11a**, mp 218–221°.[22] The ether filtrate was concentrated and the residue was rechromatographed on silica gel layer plates, using ethyl acetate as eluent, to give 85 mg (6.2%) of **13**, mp 172–173°[22] after recrystallization from ether.

When the reaction was carried out with sodium hypochlorite with the addition of tetrahydrofuran in a similar manner as described in method K, there was obtained a 8.4% yield of **11a**.

Reaction of 7a with Potassium Hypobromite. The procedure described in method O was followed except that the heating time was extended to 2 hr. The gummy material was crystallized from ether to give 0.10 g (14.8% from 0.64 g of **7a**) of **11a**, mp 222–223°.[22] Considerable amounts of **7a** and **12a** were present in the ether filtrate as determined by thin layer chromatography.

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Registry No.—**1a,** 51820-32-7; **1b,** 30008-48-1; **1c,** 32502-22-0; **2a,** 51559-71-8; **2b,** 51820-33-8; **2c,** 51820-34-9; **3a,** 51559-72-9; **3b,** 51820-35-0; **3c,** 51820-36-1; **4a,** 51820-37-2; **5a,** 51820-38-3; **5c,** 51820-39-4; **6a,** 51820-40-7; **6c,** 51820-41-8; **7a,** 51820-42-9; **7a** hydrochloride, 51820-43-0; **7b,** 51820-44-1; **7c,** 51820-45-2; **7c** hydrochloride, 51820-46-3; **9a,** 51820-47-4; **9c,** 40387-16-4; **10a,** 51820-48-5; **11a,** 20927-53-1; **11c,** 40069-75-8; **12a,** 51820-49-6; **12b,** 51820-50-9; **13,** 51820-51-0; **14,** 51820-52-1; **15,** 784-38-3; **16,** 51820-53-2; **24a,** 51820-54-3; **27c,** 51806-10-1; **28,** 21139-24-2; **29,** 51820-55-4; **30,** 20423-55-6; **31,** 51820-56-5; **32,** 51820-57-6.

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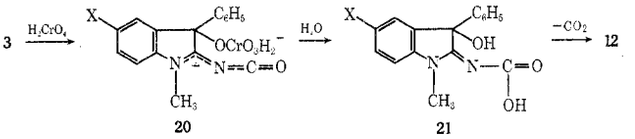
(9) In carbon tetrachloride solution the free base **7a** was shown to be present as a 85:15 mixture of the amino and the imino tautomers by nmr spectroscopy.[7]

(10) Although it is impossible to formulate a detailed mechanism for the oxidation of **3** to **12** on the basis of experimental evidence now available, we would like to propose a working hypothesis as shown by the following sequence. Obviously, this hypothesis represents only one of several possible mechanistic pathways. For general reviews of the chromic acid oxidation of C=C bonds, see (a) K. B. Wiberg, "Oxidation in Organic Chemistry," Part A, Academic Press, New York, N. Y., 1968, p 69; (b) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, p 275.



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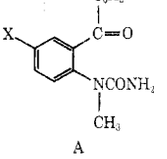
(11) In the oxidation of **3a**, similar results were realized either in aqueous acetic acid or in acetic acid containing acetic anhydride to maintain anhydrous conditions. In either case, however, water was added in order to isolate products. Therefore, as suggested by a referee, the intermediacy of urea A[18] in the sequence of reactions leading to **11** cannot be rigorously excluded.



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Quinazolines. III.[1] Curtius and Hofmann Reactions of 2′-Benzoyloxanilic Acids. Novel Syntheses of Quinazolinones

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N-Substituted 2′-benzoyloxaniloyl chlorides **2**, prepared from the reaction of the corresponding 2-aminobenzophenones **1** and oxalyl chloride, were converted through their azides **3** to quinazolinones **6** in good yields by treatment with aqueous sodium azide. N-Unsubstituted derivative **2e** gave the azide intermediate **3e**, which was shown to be identical with the product of chromic acid oxidation of the corresponding indole-2-carboxylic acid azide. For the Hofmann reaction, *N*-(2-benzoylphenyl)oxamides **7a,b,f** were prepared from the corresponding chlorides **2** by treatment with ammonia. Similar reaction of nitro compound **2c** with ammonia led to a mixture of quinazolinone **6c** and 2-hydroxyquinazoline **8**. The desired oxamide **7c**, however, was obtained by chromic acid oxidation of indole-2-carboxamide **10**. *N*-Alkyl-substituted oxamides **7a–c** were converted to the corresponding quinazolinones **6** in satisfactory yields either by treatment with aqueous sodium hypobromite in tetrahydrofuran, or with methanolic sodium hypobromite in methanol.

In an accompanying paper,[1] it was shown that 2′-benzoyloxaniloyl azides and their rearranged isocyanates were intermediates in the oxidative ring enlargement of indole-2-carboxylic acid azides and 2-isocyanatoindoles to quinazolinones. We wish to report now on the Curtius (sodium azide method)[2a] and Hofmann reactions[2b] of 2′-benzoyloxanilic acids. Although oxaniloyl azides have been reported to undergo the Curtius rearrangement in the presence of amines to give biurets,[2d] the Hofmann reaction of oxamides, which is expected to give ureas, has not been investigated.

Curtius Reaction of 2′-Benzoyloxaniloyl Chlorides 2. The required oxaniloyl chlorides **2** (Scheme I) were readily prepared from the corresponding 2-aminobenzophenones **1** by treatment with oxalyl chloride, and utilized in the next step without further purification. When a solution of N-substituted derivatives **2** in acetone was treated with aqueous sodium azide (wet method), the expected quinazolinones **6** were precipitated[3] in high yields, as shown in Table I. This was, however, preceded by the formation of another compound as could be established by thin layer chromatography. In the case of **2a**, this intermediate, urea **5a** could be isolated by carrying out the reaction at low temperature and quenching with water. However, the urea **5a** could not be purified owing to its great tendency to cyclize, although analysis of the crude product agreed with that of the assigned structure. The crude product was cyclized completely to **6a** by refluxing in toluene. The isolation of **5a** indicates that hydrolysis of the isocyanate intermediate **4** occurs prior to cyclization to **6**.

The conversion of **2a** to **6a** was also achieved, although in lower yield, by heating a solution of **2a** in toluene with powdered sodium azide[4] (dry method), a method practicable only for reactive chlorides.[2a] Under these anhydrous conditions, the formation of **6** must involve direct cyclization of **4** with elimination of carbon dioxide to give **6**.

Table I
Reactions of 2′-Benzoyloxaniloyl Chlorides with Sodium Azide

No.	Compd	R	X	Y	Method	Temp, °C	Time, hr	Product	Yield,[a] %	Mp,[b] °C	Lit. mp, °C
1	**2a**	CH_3	Cl	H	Wet	*c*	4.5	**6a**	90	224–224.5	222–223[d]
2	**2a**	CH_3	Cl	H	Dry	100	4	**6a**	36	223–224	222–223[d]
3	**2b**	CH_2-c-C_3H_5	Cl	H	Wet	*c*	4	**6b**	86	173–174	175–176[e]
4	**2c**	CH_3	NO_2	H	Wet	60[f]	3	**6c**	77	269–270	261–262[g]
5	**2d**	$(CH_2)_2OCOCH_3$	NO_2	H	Wet	60[f]	1	**6d**	73[h]	154.5–155.5[h]	155–156[i]
6	**2e**	H	Cl	F	Wet	*c*	0.5	**3e**	*j*		
7	**2e**	H	Cl	F	Dry	112	1.5	**3e** **6e**	19 4	104–106 >300	105–106[k] >300[l]

[a] Overall yield from the corresponding 2-aminobenzophenone and based on product precipitated from the reaction mixture unless otherwise stated. [b] The melting points were taken without recrystallization unless otherwise stated. [c] Room temperature. [d] Reference 5c. [e] Reference 5b. [f] Before heating, the reaction temperature was maintained at room temperature with a reaction time of 1–2 hr. [g] Reference 6. [h] Yield and melting point of the sample recrystallized once from ethanol. [i] Reference 7. [j] The ir spectrum of the reaction product indicated the presence of **3e**. [k] Reference 1. [l] K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.*, **38**, 2617 (1973).