With one exception, the *erythro* J value was larger than the *threo* value. This appears to be a rather general phenomenon.[21]

In general, the large groups in the *erythro* series appear to prefer a *trans* orientation, *e.g.*, cyclohexyl–methyl in V, and isopropyl–isopropyl in IV. In the *threo* series of compounds, the situation is complex and each case must be considered individually.

Experimental Section

The synthesis and properties of I–V have been described in earlier work.[22-25] Compound VI was prepared by the method of Curtin and Kellom[26]: mp 63–64° for each isomer.

Acknowledgments.—Compounds I–V were the generous gift of Dr. D. J. Cram. This work was supported in part by the National Science Foundation Grant GP-3551.

[21] C. A. Kingsbury, unpublished results.

[22] D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2129 (1952).

[23] D. J. Cram and F. A. Abd Elhafez, *ibid.*, **75**, 3189 (1953).

[24] D. J. Cram, H. L. Nyquist, and F. A. Abd Elhafez, *ibid.*, **79**, 2870 (1957); D. J. Cram and J. Knight, *ibid.*, **76**, 5335 (1954).

[25] D. J. Cram and J. Tadanier, *ibid.*, **81**, 2737 (1959).

[26] D. Y. Curtin and D. B. Kellom, *ibid.*, **75**, 6011 (1953).

The Synthesis and Reactions of 1-Carbamyl-11-ketoindeno[1,2-*c*]isoquinoline[1]

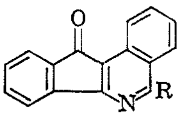
S. WAWZONEK, J. K. STOWELL, AND R. E. KARLL

Department of Chemistry, University of Iowa, Iowa City, Iowa

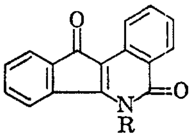
Received June 28, 1965

The reaction of phthalaldehyde with sodium cyanide formed 1-carbamyl-11-ketoindeno[1,2-*c*]isoquinoline (Ia). Evidence for this structure was the infrared spectrum, its reactions, and synthesis of several reaction products. The amide Ia was hydrolyzed to 1-carboxy-11-ketoindeno[1,2-*c*]isoquinoline (Ib) which was converted with zinc and acetic acid to the known 11H-indeno[1,2-*c*]isoquinoline. Oxidation with copper sulfate in pyridine gave 11-ketoindeno[1,2-*c*]isocarbostyril (IIa), which was synthesized by the ammonolysis of 11-ketoindeno[1,2-*c*]isocoumarin.

The reaction of phthalaldehyde with sodium cyanide was studied as a possible method for the preparation of a dibenzocyclooctane derivative. The compound actually isolated was 1-carbamyl-11-ketoindeno[1,2-*c*]isoquinoline (Ia).



Ia, $R = CONH_2$ e, $R = CN$
b, $R = COOH$ f, $R = OC_2H_5$
c, $R = COOC_2H_5$ g, $R = Cl$
d, $R = H$



IIa, $R = H$
b, $R = CH_3$

Evidence for this structure was obtained from its reactions and infrared spectrum. The latter gave absorption (in μ) at 2.95 and 3.12 for the amide hydrogens, 5.85 for the ketone group, 6.03 for the amide carbonyl, and 6.16, 6.25, 6.36, 6.42, and 6.6 for the aromatic region. Complex absorptions in the aromatic region of this type are also shown by isoquinolines.

The presence of the amide grouping was confirmed chemically by hydrolysis with sulfuric acid to acid Ib and ethanolysis by hydrogen chloride in ethanol to ester Ic. The use of hydrochloric acid alone caused hydrolysis and decarboxylation to 11-ketoindeno-[1,2-*c*]isoquinoline (Id) which formed an oxime. No drastic changes occurred in the formation of acid Ib since it was reconverted to the amide by treating the acid chloride, formed with thionyl chloride, with ammonia.

Amide Ia behaved normally with dehydrating agents and was converted to the nitrile Ie by either phosphorus pentoxide or a mixture of benzoyl chloride in pyridine. This compound (Ie) showed a weak absorption maximum at 4.45 μ for the cyano group in its infrared spectrum and, when treated with sodium ethoxide, underwent a nucleophilic substitution similar to that observed for 1-substituted isoquinolines[2,3] and gave the ethoxy compound If.

The ethoxy compound If was easily cleaved with alkali to the isocarbostyril IIa which could also be prepared by the action of alkali on the cyano derivative Ie and the oxidation of the amide Ia in pyridine by copper sulfate. Rearrangements in these reactions were precluded by the synthesis of the nitrile Ie from the isocarbostyril IIa; treatment of the latter with phosphorus oxychloride gave the chloro compound Ig which, upon heating with cuprous cyanide, gave the nitrile Ie.

The isocarbostyril IIa was soluble in alcoholic alkali and converted in this medium by dimethyl sulfate to the N-methylisocarbostyril IIb. The latter was cleaved by alcoholic alkali to 2-(carboxyphenyl)-1,3-indandione which, upon treatment with acid, gave 11-ketoindeno[1,2-c]isocoumarin.[4] The isolation of the latter suggested that an isocarbostyril ring system was involved in the compounds reported. The isocarbostyril structure (IIa) was confirmed by its synthesis from the isocoumarin and ammonia and by the reductive decarboxylation of the acid Ib with zinc and acetic acid to the known 11H-indeno[1,2-*c*]isoquinoline.[5]

Further reactions of the isocarbostyril IIa were in agreement with its structure. Reduction by zinc and alkali gave the 11-hydroxy compound III, and oxida-

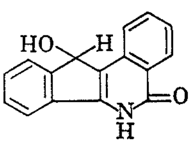
[1] Abstracted in part from the Ph.D. theses of J. K. Stowell, June 1965, and R. E. Karll, June 1949.

[2] S. Gabriel, *Ber.*, **19**, 830, 2354 (1886).

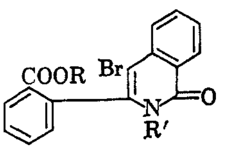
[3] F. Damerow, *ibid.*, **27**, 2232 (1894).

[4] M. Pailer, H. Worthen, and A. Meller, *Monatsh.*, **92**, 1037 (1961).

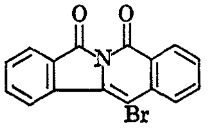
[5] J. N. Chatterjea and H. Mukherjee, *J. Indian Chem. Soc.*, **37**, 379 443 (1960).



III



IVa, R = R' = H
b, R = CH_3; R' = H
c, R = H_1; R' = CH_3
d, R = R = CH_3

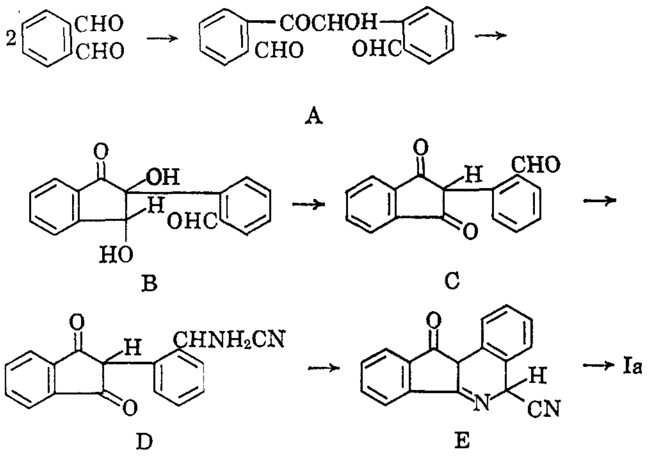


V

tion in alkali with bromine gave the brominated acid IVa which had an infrared spectrum practically identical with authentic 3-(2-carboxyphenyl)isocarbostyril.[6] This acid (IVa) formed an ester (IVb) when treated with methanolic hydrogen chloride and gave the N-methyl derivative IVc when treated with dimethyl sulfate in alkali. The latter (IVc) formed a methyl ester (IVd) and, upon heating at its melting point, unexpectedly cyclized to the N-methylisocarbostyril IIb. The mechanism of this cyclization is not apparent at the present time.

Pyridine and benzoyl chloride converted the brominated isocarbostyril IVa into 12-bromoisoindolo-[2,1-*b*]isoquinoline-5,7-dione (V) which was synthesized by treating the parent compound[6] with bromine in acetic acid.

The formation of 1-carbamyl-11-ketoindeno[1,2-*c*]-isoquinoline (Ia) from phthalaldehyde and sodium cyanide suggests that the reaction starts with a normal benzoin condensation and is followed by an intramolecular cyclization and loss of water in the indandione C.



Further reaction of the free aldehyde group in C occurs with cyanide ion and ammonia, generated in the solution by the hydrolysis of cyanide ion or by-products, and forms an aminonitrile (D) which can cyclize to the dihydroisoquinoline E. Hydrolysis of the nitrile followed by air oxidation would yield the final product Ia.

The proposed mechanism is consistent with the low yield of amide (Ia) formed; ammonia liberated early in the reaction should react preferentially with the phthalaldehyde[7] and form the tars obtained as a by-product.

Experimental Section[8]

1-Carbamyl-11-ketoindeno[1,2-*c*]isoquinoline (Ia).—Phthalaldehyde (4 g) was dissolved in 12 ml of ethanol and refluxed with sodium cyanide (0.9 g) and 3 ml of 2 *N* sodium carbonate for 1 hr. A golden yellow solid slowly precipitated from the dark solution near the end of the hour. The mixture was cooled overnight at 10°. The yellow solid was filtered and washed with alcohol and water. Recrystallization from dimethylformamide gave 0.59 g of yellow needles melting at 327–328°. *Anal.* Calcd for $C_{17}H_{10}O_2N_2$: C, 74.45; H, 3.65; N, 10.22. Found: C, 74.75; H, 3.69; N, 9.96. The infrared spectrum showed bands (in μ) at 2.95 and 3.12 (N-H), 5.87 and 6.03 (C=O), and 6.16, 6.25, 6.36, 6.42, and 6.6 (aromatic). The remainder of the product was a dark tar which could not be crystallized.

1-Carboxy-11-ketoindeno[1,2-*c*]isoquinoline (Ib).—The isoquinoline Ia (1.4 g) was heated at 100° in 100 ml of 65% sulfuric acid for 24 hr and then allowed to stand for 48 hr at room temperature. The solid, which crystallized, was filtered and washed with water. Recrystallization from chloroform gave 0.9 g of orange needles melting at 213–214°. *Anal.* Calcd for $C_{17}H_9O_3N$: C, 74.18; H, 3.27; N, 5.09. Found: C, 73.88; H, 3.43; N, 4.91. The infrared spectrum gave bands (in μ) at 3.10–4.00 (OH), 5.91 (C=O), and 6.20, 6.29, 6.44, and 6.66 (aromatic).

The acid Ib (0.1 g) was heated on a steam bath with 5 ml of thionyl chloride until the excess thionyl chloride evaporated. The residue was cooled to −80° and treated with liquid ammonia. The resulting mixture was allowed to warm to room temperature and stand until all the excess ammonia had evaporated. The residue was recrystallized from dimethylformamide and gave 0.09 g of yellow needles identical with the amide Ia.

Reduction of 1-Carboxy-11-ketoindeno[1,2-*c*]isoquinoline (Ib).—The acid Ib (1 g) was refluxed in 60 ml of acetic acid and 10 ml of water with excess zinc dust. When the solution became colorless, it was cooled and filtered from the excess zinc. The solution, when neutralized with ammonium hydroxide, gave a white precipitate. The white solid, after recrystallization from a mixture of benzene and hexane, weighed 0.4 g and melted at 162–163°. It was identical with an authentic sample of 11H-indeno[1,2-*c*]isoquinoline.[5]

11-Ketoindeno[1,2-*c*]isoquinoline (Id).—The isoquinoline Ia (1 g) was refluxed in a mixture of 50 ml of acetic acid and 30 ml of concentrated hydrochloric acid for 72 hr. After the solution was cooled and filtered, it was diluted with an equal volume of water and allowed to stand for 24 hr. The product, when recrystallized from hexane, gave a light yellow solid (0.6 g) melting at 199–200°. *Anal.* Calcd for $C_{16}H_9ON$: C, 83.12; H, 3.90; N, 6.06. Found: C, 82.99; H, 4.03; N, 6.09. The infrared spectrum showed absorption (in μ) at 5.9 (C=O) and 6.19, 6.21, 6.42, and 6.77 (aromatic).

The oxime was formed by refluxing the ketone Id (0.49 g) with hydroxylamine hydrochloride (0.15 g) and sodium acetate trihydrate (0.30 g) in ethanol (85 ml) for 17 hr. The crystals (0.16 g) formed upon cooling melted at 255° with decomposition after one crystallization from ethyl acetate. *Anal.* Calcd for $C_{16}H_{10}ON_2$: C, 78.24; H, 4.38. Found: C, 78.05; H, 4.07.

1-Carbethoxy-11-ketoindeno[1,2-*c*]isoquinoline (Ic).—The isoquinoline Ia (1 g) was refluxed for 24 hr in 400 ml of absolute ethanol saturated with hydrogen chloride. The resulting solution was concentrated to 50 ml and diluted with water. The precipitate was filtered and washed with dilute sodium hydroxide and water. The solid, when recrystallized from ethanol, weighed 0.36 g and melted at 181–182°. *Anal.* Calcd for $C_{19}H_{13}O_3N$: C, 75.25; H, 4.29; N, 4.62. Found: C, 75.30; H, 4.40; N, 4.80. The infrared spectrum showed peaks (in μ) at 5.81 (C=O) and 6.20, 6.22, and 6.44 (aromatic). The ester was converted to the acid Ib by heating with dilute alkali.

1-Cyano-11-ketoindeno[1,2-*c*]isoquinoline (Ie). A.—The isoquinoline Ia (0.3 g) was mixed with 0.3 g of phosphorus pentoxide in a sublimation tube and heated at 300°. The solid which sublimed from the melt was recrystallized from chloroform and gave an orange solid (0.25 g) melting at 273–274°. *Anal.* Calcd for $C_{17}H_8ON_2$: C, 79.68; H, 3.12; N, 10.93. Found: C, 79.69; H, 3.10; N, 10.63. The infrared spectrum showed peaks (in μ) at 4.45 (CN), 5.84 (C=O), and 6.19, 6.43, and 6.64 (aromatic).

B.—The isoquinoline Ia (1 g) was dissolved by heating in pyridine (50 ml) containing benzoyl chloride (10 ml). Cooling the solution gave the nitrile Ie, yield 0.99 g. The cyano com-

---

[6] J. Ephraim, *Ber.*, **24**, 2820 (1891).

[7] J. Thiele and E. Winter, *Ann.*, **311**, 360 (1900).

[8] All melting points are corrected. Infrared spectra were determined on Nujol mulls.

pound was converted to the isocarbostyril IIa when it was heated with dilute alkali.

1-Ethoxy-11-ketoindeno[1,2-*c*]isoquinoline (If).—The cyanoisoquinoline Ie (0.5 g) was dissolved in 150 ml of absolute ethanol pretreated with sodium. The solution was allowed to stand at room temperature for 24 hr, and the solid which formed was recrystallized from chloroform: yield 0.4 g, mp 182–183°. *Anal.* Calcd for $C_{18}H_{13}O_2N$: C, 78.54; H, 4.73; N, 5.09. Found: C, 78.79; H, 4.76; N, 5.09. The infrared spectrum showed absorption (in μ) at 5.87 (C=O) and 6.14, 6.24, 6.42, and 6.60 (aromatic).

The nmr spectrum in deuterated chloroform with tetramethylsilane as a reference showed a triplet from 1.43 to 1.67 ppm for three methyl protons, a quartet from 4.50 to 4.90 ppm for two methylene protons, and a broad region from 7.30 to 8.40 ppm for eight aromatic protons.

11-Ketoindeno[1,2-*c*]isocarbostyril (IIa). A.—The ethoxy compound If (0.1 g) was dissolved in 15 ml of dilute potassium hydroxide containing 5 ml of ethanol by warming the solution. The red solution was diluted with 20 ml of water, filtered, and acidified with dilute hydrochloric acid. The precipitate upon recrystallization from acetic acid gave an orange-red solid (0.06 g) melting at 375–376°. *Anal.* Calcd for $C_{16}H_9O_2N$: C, 77.73; H, 3.65; N, 5.67. Found: C, 77.66; H, 3.63; N, 5.78. The infrared spectrum showed absorption (in μ) at 3.10–3.70 (N–H), 5.88, and 6.05 (C=O), and 6.16, 6.31, 6.43, and 6.52 (aromatic).

B.—The isoquinoline Ia (1.5 g) was refluxed in a mixture of 250 ml of pyridine and 100 ml of water containing 30 g of copper sulfate for 30 hr. The solution was poured into 520 ml of 6 *N* hydrochloric acid, and the orange precipitate was filtered and washed with water. The solid was dissolved in 2% potassium hydroxide solution containing some alcohol and filtered to remove the unchanged isoquinoline Ia. The filtrate was acidified, and the precipitate was recrystallized from acetic acid. The orange crystals (1.2 g) melted at 375–376° and were identical with the product in A.

C.—11-Ketoindeno[1,2-*c*]isocoumarin[4] (0.7 g) was heated in a bomb with 75 ml of absolute ethanol saturated with ammonia at 150° for 5 hr. The resulting ethanol solution was diluted with 75 ml of water and acidified with hydrochloric acid. The orange solid (0.63 g) melted at 375–376° and was identical with the product in A.

6-Methyl-11-ketoindeno[1,2-*c*]isocarbostyril (IIb).—The isocarbostyril IIa (1 g) was dissolved in 300 ml of 2% potassium hydroxide solution containing 30 ml of methanol. Excess dimethyl sulfate was added with vigorous stirring and, after 2 hr, the solution was warmed on a steam bath for 1 hr. After cooling, the red solid was filtered and washed with dilute alkali and water. The red solid, when recrystallized from benzene, weighed 0.65 g and melted at 243–243.5°. *Anal.* Calcd for $C_{17}H_{11}O_2N$: C, 78.16; H, 4.21; N, 5.36. Found: C, 78.33; H, 4.45; N, 5.34. The infrared spectrum showed peaks (in μ) at 5.90 and 6.00 (C=O) and 6.20, 6.31, 6.44, and 6.73 (aromatic).

The isocarbostyril IIb (1 g) was refluxed in 100 ml of ethanol containing 2.6 g of sodium hydroxide for 1 hr. The resulting solution was cooled, diluted with 200 ml of water, and allowed to stand for 3 hr. The solution was filtered, acidified, and cooled for 24 hr. The solid (0.5 g) which crystallized was identical with an authentic sample of 2-(*o*-carboxyphenyl)-1,3-indandione.[4]

This compound (0.5 g), when heated on a steam bath in 50 ml of concentrated hydrochloric acid, gave an orange solid. Recrystallization from benzene gave light orange needles (0.4 g) melting at 261–262°, identical with an authentic sample of 11-ketoindeno[1,2-*c*]isocoumarin.[4]

11-Chloro-11-ketoindeno[1,2-*c*]isoquinoline (Ig).—The isocarbostyril IIa (0.7 g) was refluxed with 20 ml of phosphorus oxychloride for 2 hr. The green solution was cooled and poured over cracked ice. The resulting solid was filtered and washed with dilute potassium hydroxide solution to remove any unchanged isocarbostyril IIa. The solid, when recrystallized from benzene, weighed 0.61 g and melted at 244–245°. *Anal.* Calcd for $C_{16}H_8ONCl$: C, 72.32; H, 3.01; N, 5.27. Found: C, 72.37; H, 3.00; N, 5.21. The infrared spectrum showed absorption (in μ) at 5.81 and 5.89 (C=O) and 6.19, 6.23, 6.39, 6.48, and 6.66 (aromatic).

The chloro compound Ig (0.1 g) was mixed with 0.1 g of cuprous cyanide and heated until liquid. The mixture was kept in a molten state for 30 min. After cooling, the residue was extracted with benzene. The benzene solution upon evaporation to dryness gave a solid which was recrystallized twice from chloroform. The orange crystals (0.06 g) were identical with the cyano compound Ie.

11-Hydroxyindeno[1,2-*c*]isocarbostyril (III).—The isocarbostyril IIa (0.3 g) was refluxed in a mixture of acetic acid (100 ml) and water (5 ml) with excess zinc dust until the solution was colorless. The solution was cooled, filtered, and diluted with water (100 ml). The resulting white solid was recrystallized from acetic acid: yield 0.25 g, mp 364–365° dec. *Anal.* Calcd for $C_{16}H_{11}O_2N$: C, 77.11; H, 4.42; N, 5.62. Found: C, 76.95; H, 4.66; N, 5.40. The infrared spectrum showed absorption (in μ) at 2.92 (OH), 3.25–3.55 (NH), 6.10 (C=O), and 6.18, 6.23, 6.30, and 6.41 (aromatic).

4-Bromo-3-(*o*-carboxyphenyl)isocarbostyril (IVa).—The isocarbostyril IIa (0.5 g) was dissolved in a mixture of 50 ml of 5% potassium hydroxide solution and 20 ml of methanol. The resulting red solution was treated with 1.1 ml of a bromine solution prepared from 1 ml of bromine and 10 ml of methanol. The color of the solution became light yellow. After filtration, the solution was acidified with dilute hydrochloric acid. Recrystallization of the solid from dilute ethanol gave 0.56 g of a white solid melting at 265–266° with decomposition. *Anal.* Calcd for $C_{16}H_{10}O_3NBr$: C, 55.81; H, 2.91; N, 4.07. Found: C, 55.97; H, 3.18; N, 4.04. The infrared spectrum showed absorption (in μ) at 3.20–4.20 (O–H, N–H), 5.10–5.50, 5.95 (C=O), and 6.15, 6.20, 6.32, and 6.48 (aromatic).

4-Bromo-3-(*o*-carbomethoxyphenyl)isocarbostyril (IVb).—The acid IVa (0.1 g) was dissolved in 40 ml of anhydrous methanol containing hydrogen chloride. The solution was allowed to stand for 24 hr, concentrated to 10 ml, and diluted with water (20 ml). Recrystallization of the solid from dilute methanol gave 0.09 g of a white solid melting at 269–270°. *Anal.* Calcd for $C_{17}H_{12}O_3NBr$: C, 56.98; H, 3.35; N, 3.91. Found: C, 56.86; H, 3.54; N, 3.81. The infrared spectrum showed absorption (in μ) at 5.80 and 6.02 (C=O) and 6.15, 6.22, 6.35, and 6.45 (aromatic).

4-Bromo-2-methyl-3-(*o*-carboxyphenyl)isocarbostyril (IVc).—The acid IVa (0.35 g) was dissolved in 50 ml of 2 *N* sodium hydroxide solution, and dimethyl sulfate (1 ml) was added slowly with vigorous stirring. The solution was kept basic by the addition of more alkali and allowed to stand for 2 hr. The solution was filtered and acidified with dilute hydrochloric acid. Recrystallization of the precipitate from dilute ethanol gave 0.35 g of a white solid melting at 277–278° with decomposition. *Anal.* Calcd for $C_{17}H_{12}O_3NBr$: C, 56.98; H, 3.35; N, 3.91. Found: C, 56.73; H, 3.39; N, 3.85. The infrared spectrum showed absorption (in μ) at 3.10–3.70 (O–H), 5.89 (C=O), and 6.20, 6.30, 6.38, and 6.42 (aromatic).

4-Bromo-2-methyl-3-(*o*-carbomethoxyphenyl)isocarbostyril (IVd).—The N-methyl acid IVc (0.1 g) was dissolved in 20 ml of anhydrous methanol containing hydrogen chloride and allowed to stand for 24 hr. The solution was concentrated to 10 ml and diluted with water. Recrystallization of the precipitate from dilute ethanol gave 0.1 g of a white solid melting at 189–190°. *Anal.* Calcd for $C_{18}H_{14}O_3NBr$: C, 58.06; H, 3.76; N, 3.76. Found: C, 58.17; H, 3.78; N, 3.79. The infrared spectrum showed absorption (in μ) at 5.82 and 6.04 (C=O) and 6.20, 6.29, and 6.44 (aromatic).

Pyrolysis of 4-Bromo-2-methyl-3-(*o*-carboxyphenyl)isocarbostyril (IVc).—The N-methyl acid IVc (0.2 g) was heated in a sublimator at its melting point for 45 min. The red solid which sublimed melted at 243–243.5° after one recrystallization from chloroform and was identical with 6-methyl-11-ketoindeno-[1,2-c]isocarbostyril: yield 0.1 g.

12-Bromoisoindolo[2,1-*b*]isoquinoline-5,7-dione (V). A.—The acid IVa (0.46 g) was dissolved in pyridine (15 ml), and benzoyl chloride (1.5 ml) was added dropwise. The solution was heated on a steam bath for 30 min and poured into 30 ml of water. A solid slowly precipitated from the solution which, after crystallization from dilute methanol, gave 0.42 g of crystals melting at 263–264°. *Anal.* Calcd for $C_{16}H_8O_2NBr$: C, 58.90; H, 2.45; N, 4.29. Found: C, 59.05; H, 2.68; N, 4.35. The infrared spectrum showed absorption (in μ) at 5.64 and 5.91 (C=O) and 6.20 and 6.25 (aromatic).

B.—The isoindolo compound[6] (0.4 g) was dissolved in 20 ml of acetic acid and treated with several drops of bromine. The resulting solution was allowed to stand for 2 hr and then diluted with 40 ml of water. Recrystallization of the precipitate from dilute methanol gave 0.4 g of a crystalline solid melting at 263–264° and identical with the product formed in A.