Nucleophilic Displacement of Aromatic Fluorine, Part III (1), Indoloquinolines and Benzofuranoquinolines

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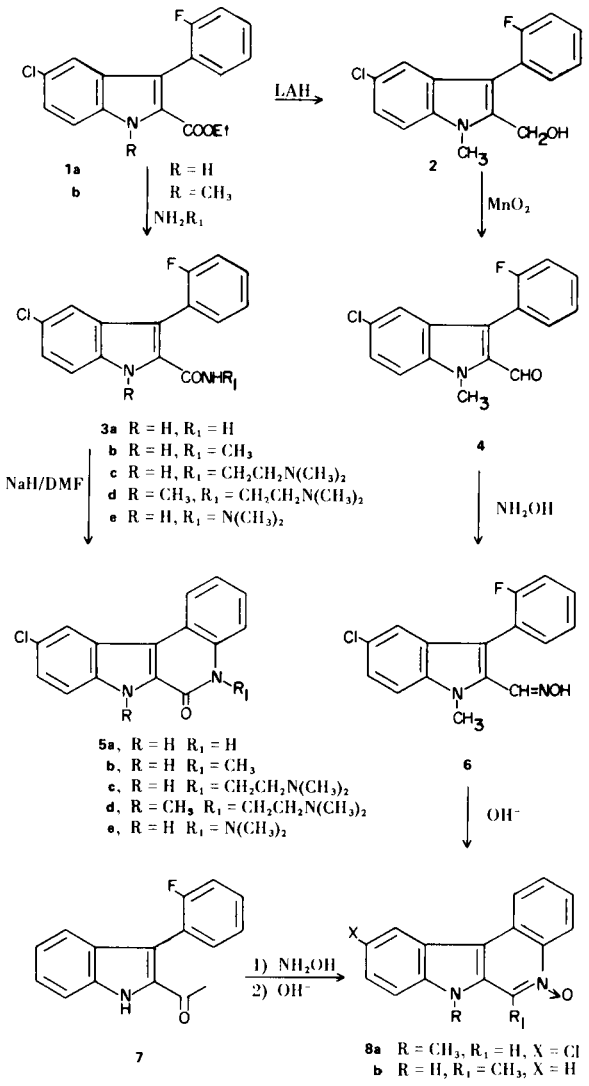
Variously substituted indolo[2,3-*c*]quinolines, benzofurano[2,3-*c*]quinolines and their positional isomers indolo[3,2-*c*]quinolines and benzofurano[3,2-*c*]quinolines respectively, were prepared from both indole and quinoline derivatives by intramolecular nucleophilic displacement of aromatic fluorine. The formation of an indolo[2,3-*d*]benzazepine was also observed.

The utilization of the intramolecular displacement of activated aromatic fluorine for the synthesis of benzisoxazoles (2) and indazoles (1) has been illustrated in previous publications. We now wish to report the extention of this reaction to the preparation of indoloquinolines and benzofuranoquinolines. The indoles **1** (Scheme I), the benzophenone **17** and the phenylacetanilides **18** (Scheme IV) provided the starting materials for the chemical transformations described below.

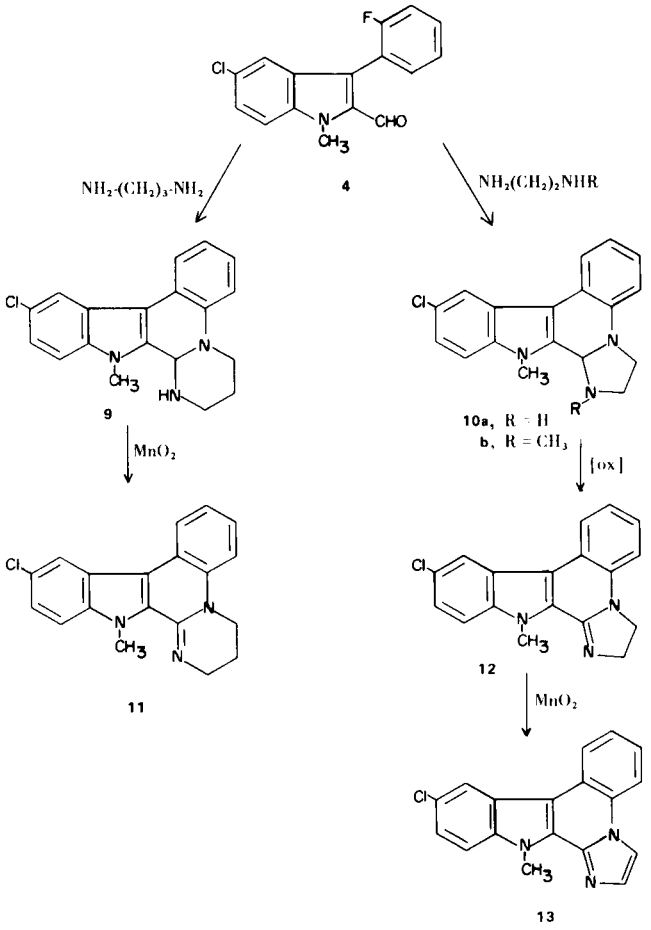
The indole-2-carboxamides **3** (3), (4) (Scheme I) were found to cyclize in nearly quantitative yield to the indolo[2,3-*c*]quinolin-6(5*H*)ones **5** (5) by treatment with sodium hydride in refluxing dimethylformamide. The indoloquinoline *N*-oxides **8** were similarly obtained by cyclization of either the oxime **6** or the oxime of the 2-acetylindole **7** with ethanolic sodium hydroxide. The oxime **6** was prepared in the usual manner from the indole-2-carboxaldehyde **4**, which, in turn, was accessible from the corresponding ester **1b** *via* the alcohol **2**. The 2-acetylindole **7** was prepared from aniline and ethyl 2-acetyl-3-(2-fluorophenyl)propionate by a modified Japp-Klingemann reaction according to the procedure of Manske *et al.*, (6). In analogy to a procedure reported by Garcia *et al.*, (7) the imidazoindoloquinoline **12** (Scheme II) was obtained by heating the aldehyde **4** with ethylenediamine. The primary product of this reaction, the corresponding dihydro derivative **10a**, was neither isolated nor characterized due to its susceptibility to air oxidation. The corresponding *N*-methyl derivative **10b**, prepared from the aldehyde **4** and *N*-methylethylenediamine, was more resistant to oxidation and was therefore fully characterized. It was interesting to note that compound **9**, which was obtained from the reaction of the aldehyde **4** with 1,3-diaminopropane was also less susceptible to air oxidation and could be isolated without difficulties. Compound **9** was readily converted to com-

(Scheme I)



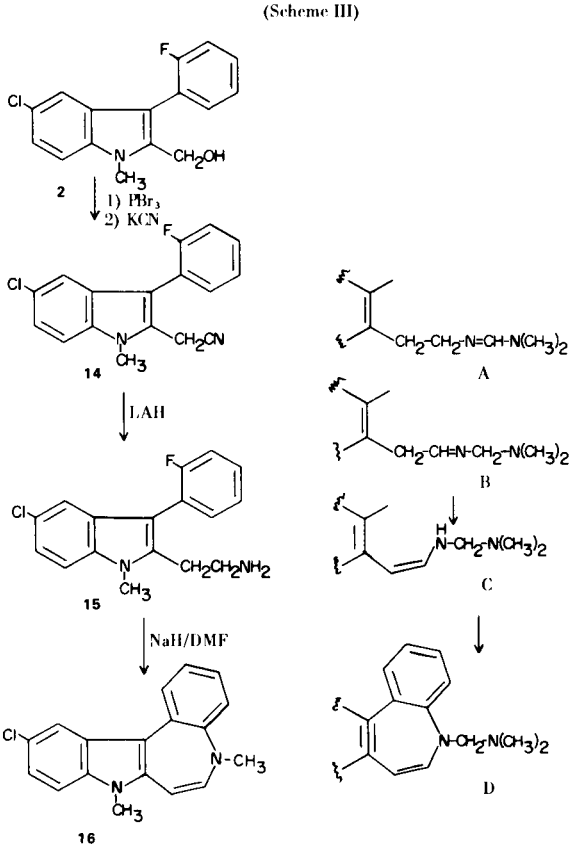
pound **11** by stirring with activated manganese dioxide at room temperature. The same reagent was also used successfully to dehydrogenate compound **12** to the imidazo derivative **13**.

(Scheme II)



In the examples discussed above, the displacement of the fluorine was facilitated by an electron withdrawing carbonyl function or its equivalent. To find out whether the indole ring itself would provide enough activation for easy displacement of the fluorine, compound **15** was prepared as shown in Scheme III. The carbinol **2** was converted to the acetonitrile **14** *via* the corresponding bromide. Reduction of the nitrile with lithium aluminum hydride led to the amine **15** which was treated with sodium hydride in boiling dimethylformamide. The only product isolated was found to be the benzazepinoindole **16** (12.5% yield by chromatography of the reaction mixture). The structure of **16** was derived from an interpretation of the analytical and spectral data. The formation of **16** is difficult to explain but could be

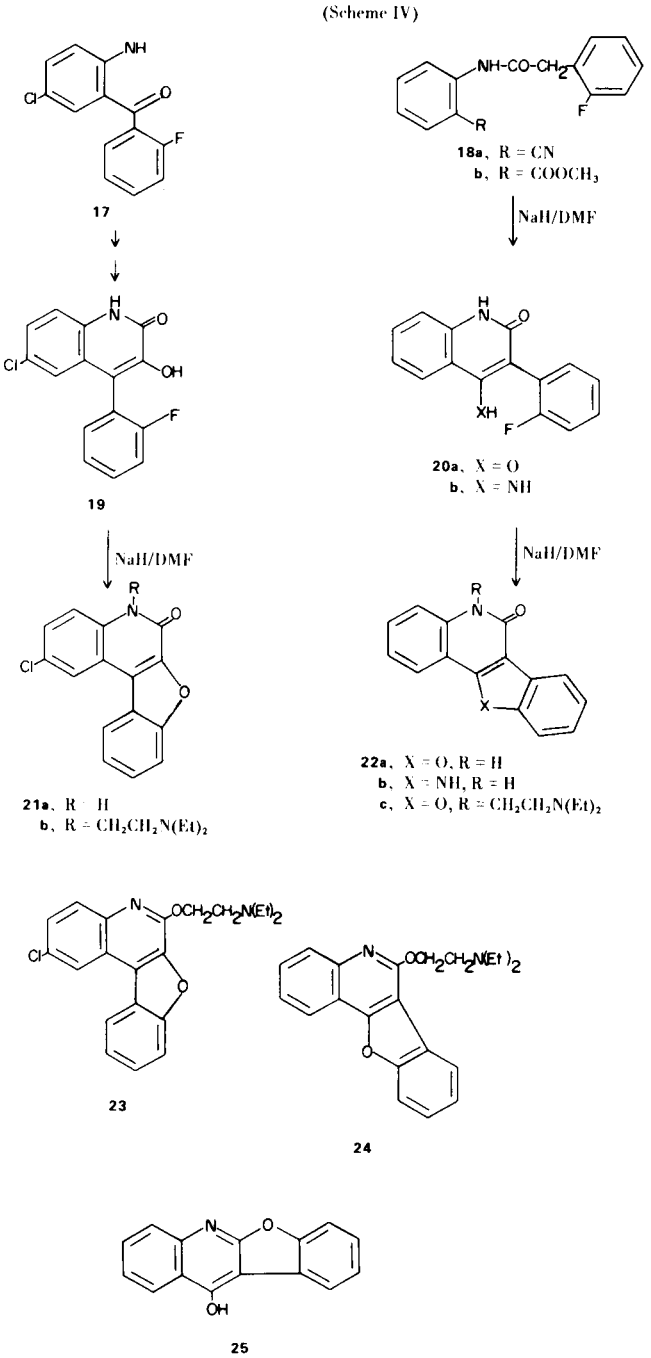
(Scheme III)



rationalized as proceeding through the intermediates **A** to **D** as shown in Scheme III. It seems likely that the additional activation of the fluorine resulting from a rearrangement of the amidine **A** to the vinylamine **C** is necessary for a successful displacement. The benzofurano-[2,3-*c*]quinolin-6(5*H*)one, **21a** (Scheme IV) was obtained by treating the hydroxyquinolone **19** with sodium hydride in refluxing dimethylformamide. The preparation of compound **19** from the benzophenone **17** has been reported in a previous publication (8). The very insoluble compound **21a** was converted to the more soluble basic derivative **21b** by alkylation of the sodium salt with 2-diethylaminoethyl chloride. Alkylation on oxygen leading to compound **23** was observed only to a small extent. The isomeric benzofurano[3,2-*c*]quinolin-6(5*H*)-one **22a** was readily accessible from the 3-(2-fluorophenyl)-4-hydroxyquinoline **20a** which was prepared by base catalized cyclization of the anthranilate **18a**. Structure **25**, considered as an alternative to **22a**, was incompatible with the spectral data. Again, alkylation of **22a** with 2-diethylaminoethylchloride yielded predominantly the *N*-alkylated derivative **22c** together with a small amount of compound **24**.

Ring closure of the 3-(2-fluorophenyl)-4-aminoquinolone **20b** under similar conditions led to the isosteric

(Scheme IV)



indolo[3,2-c]quinoline **22b**. This compound was obtained in one step from the anthranilonitrile **18b** without isolation of **20b**.

In both the indoles and the quinolines the nucleophilic displacement of the fluorine in the phenyl moiety was facilitated by electron withdrawing functions attached or incorporated into the heterocycle. It should, in general, be possible to extend this ring closure to other systems which have the sterical requirements and similar activation of the fluorine towards nucleophilic displacement, provided that the end products are capable of withstanding the reaction conditions.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus or on a Reichert hot stage microscope. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded on a Varian A-60 or Varian T-60 instrument with TMS as internal standard. Ir spectra were determined on a Beckman 112-9 spectrometer and mass spectra on a CEC-110 B instrument. Silica gel Merck (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying purposes.

Ethyl 5-Chloro-3-(2-fluorophenyl)-1-methylindole-2-carboxylate (**1b**).

Potassium *t*-butoxide, 15 g., was added to a solution of 32 g. of ethyl 5-chloro-3-(2-fluorophenyl)indole-2-carboxylate (**1a**) (3) in 200 ml. of dimethylformamide. After stirring for 5 minutes, 12.5 ml. of dimethylsulfate was added and stirring was continued for 30 minutes. The mixture was diluted with ice/water and the precipitated solid was collected, washed with water and recrystallized from ethanol to yield 24 g. (72%) of product with m.p. 78-81°.

Anal. Calcd. for $C_{18}H_{15}FClNO_2$: C, 65.2; H, 4.6; N, 4.2. Found: C, 65.2; H, 4.4; N, 4.5.

5-Chloro-3-(2-fluorophenyl)-2-hydroxymethyl-1-methylindole (**2**).

A solution of **1b**, 16.5 g., was added in portions to a suspension of 5 g. of lithium aluminum hydride in 200 ml. of ether, cooled to 0°. Following addition, the mixture was stirred for 30 minutes at room temperature and hydrolyzed by slowly adding 25 ml. of water. The inorganic material was filtered and washed with benzene. The filtrate was dried and evaporated. Crystallization of the residue from methylene chloride/hexane yielded 13 g. (90%) of product with m.p. 122-124° after recrystallization from the same solvent mixture.

Anal. Calcd. for $C_{16}H_{13}FClNO$: C, 66.3; H, 4.5; N, 4.8. Found: C, 66.3; H, 4.3; N, 5.0.

5-Chloro-3-(2-fluorophenyl)-*N*-methylindole-2-carboxamide (**3b**).

A mixture of 57.9 g. (0.2 mole) of 5-chloro-3-(2-fluorophenyl)-indole-2-carboxylic acid (3), 50 g. (0.24 mole) of phosphorus pentachloride and 1 l. of methylene chloride was stirred at room temperature for 20 minutes. An aqueous solution of methylamine was then added with ice cooling until the reaction mixture was alkaline. The product was precipitated by addition of hexane and collected. Recrystallization from methylene chloride/ethanol yielded 42.3 g. (70%) of product with m.p. 218-221°.

Anal. Calcd. for $C_{16}H_{12}ClFN_2O$: C, 63.5; H, 4.0; N, 9.3. Found: C, 63.5; H, 4.0; N, 9.3.

5-Chloro-*N*-dimethylamino-3-(2-fluorophenyl)indole-2-carboxamide (**3e**).

A mixture of 14.5 g. (0.05 mole) of 5-chloro-3-(2-fluorophenyl)indole-2-carboxylic acid (3) and 125 ml. of thionyl chloride was refluxed for 2 hours. The excess reagent was removed under reduced pressure, at the end azeotropically with benzene. The remaining acid chloride was dissolved in 100 ml. of methylene chloride. This solution was added to a stirred solution of 6 g. (0.1 mole) of unsymmetrical dimethylhydrazine in 250 ml. of

methylene chloride. After addition, the reaction mixture was stirred for 15 minutes at room temperature and was washed with water. The methylene chloride was dried and concentrated to yield 15.9 g. (75%) of product with m.p. 203-206°. Recrystallization from methylene chloride/ethanol raised the m.p. to 214-216°; uv: λ max 232 mμ (ε, 32,800) 302 (15,300); ir (potassium bromide): 3250 cm^{-1} (NH) 1650 (CON).

Anal. Calcd. for $C_{17}H_{15}ClFN_3O$: C, 61.5; H, 4.6; N, 12.8. Found: C, 61.8; H, 4.7; N, 12.7.

5-Chloro-*N*-(2-dimethylaminoethyl)-3-(2-fluorophenyl)indole-2-carboxamide (**3c**).

A solution of the acid chloride in methylene chloride was prepared as described in example **3e** from 29 g. of 5-chloro-3-(2-fluorophenyl)indole-2-carboxylic acid and 250 ml. of thionyl chloride. It was added to a stirred solution of 50 ml. of (2-dimethylamino)ethylamine in 200 ml. of methylene chloride. After stirring for 10 minutes, the methylene chloride was washed with 10% aqueous sodium carbonate and water, was dried and evaporated. The remaining crystals were slurried with ether and were collected to yield 25 g. (69%) of product with m.p. 229-231°. For analysis it was recrystallized from benzene/ethanol, m.p. 234-236°.

Anal. Calcd. for $C_{19}H_{19}ClFN_3O$: C, 63.4; H, 5.3; N, 11.7. Found: C, 63.5; H, 5.4; N, 12.0.

5-Chloro-*N*-(2-dimethylaminoethyl)-3-(2-fluorophenyl)-1-methylindole-2-carboxamide (**3d**).

A mixture of 30.3 g. (0.1 mole) of 5-chloro-3-(2-fluorophenyl)-1-methylindole-2-carboxylic acid (m.p. 232-234°, obtained by hydrolysis of corresponding ester), 100 ml. of methylene chloride and 25 ml. of thionylchloride was refluxed for 6 hours. After evaporation the residue was dissolved in methylene chloride and added to a solution of 20 ml. of 2-dimethylaminoethylamine in 100 ml. of methylene chloride. One hundred ml. of 10% aqueous sodium carbonate was then added and the two phase system was stirred for 30 minutes at room temperature. The organic layer was separated, dried and evaporated. Crystallization of the residue from ether/methylene chloride/hexane yielded 29 g. (77.5%) of product with m.p. 95-100°. For analysis it was recrystallized from ether/hexane, m.p. 100-101°.

Anal. Calcd. for $C_{20}H_{21}ClFN_3O$: C, 64.3; H, 5.7; N, 11.2. Found: C, 64.5; H, 5.8; N, 11.3.

5-Chloro-3-(2-fluorophenyl)-1-methylindole-2-carboxaldehyde (**4**).

A solution of 10 g. of **2** in 300 ml. of methylene chloride was treated with 100 g. of manganese dioxide added in 3 portions over a 6 hour period. The suspension was stirred overnight and then filtered through celite. The filtrate was evaporated and the residue was crystallized from ethanol to yield 8.2 g. (82%) of aldehyde with m.p. 98-100° after recrystallization from ethanol; uv: λ max 249 mμ (ε, 24,800), 317 (20,650), sh 351 (6,800); ir (chloroform): 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{11}ClFNO$: C, 66.8; H, 3.8; N, 4.9. Found: C, 66.7; H, 3.8; N, 4.9.

10-Chloro-7*H*-indolo[2,3-*c*]quinolin-6(5*H*)one (**5a**), (**5a**).

Sodium hydride suspension (50% in mineral oil), 14.4 g., (0.3 mole) was washed with hexane and was added to a solution of 29 g. (0.1 mole) of 5-chloro-3-(2-fluorophenyl)indole-2-carboxamide (**3a**) in 800 ml. of dimethylformamide. The mixture was stirred under nitrogen and was gradually heated to reflux for 10 minutes.

The product was crystallized from the cool reaction mixture by addition of water. It was collected, washed with water, methanol and ether to leave 26.6 g. (98%) with m.p. 334-336°. The analytical sample was recrystallized repeatedly from methylene chloride/methanol, m.p. 348-350°; uv: λ max 223 mμ (ε, 27,100), 237 (32,400), 250 (41,350), 257 (42,900), 275 (18,000), 297 (9,100), 310 (12,200), 325 (7,500), 338 (12,300), 355 (21,800); ir (potassium bromide): 3425 cm^{-1}, 3350, 3150 (NH) 1640 (CO).

10-Chloro-5-methyl-7*H*-indolo[2,3-*c*]quinolin-6(5*H*)one (**5b**).

A mixture of 6.05 g. (0.02 mole) of **3b**, 2.9 g. (0.06 mole) of sodium hydride suspension (50% in mineral oil) and 30 ml. of dimethylformamide was heated to reflux for 10 minutes under an atmosphere of nitrogen. The reaction mixture was poured into water. The precipitated product was collected, washed with water and methanol and was recrystallized from dimethylformamide to yield 4 g. (71%) with m.p. > 360°; ir (potassium bromide): 3200 cm^{-1} (NH) 1640 (C=O).

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: C, 68.0; H, 3.9; N, 9.9. Found: C, 68.1; H, 3.9; N, 10.0.

10-Chloro-5-(2-dimethylaminoethyl)-7*H*-indolo[2,3-*c*]quinolin-6-(5*H*)one (**5c**).

Sodium hydride suspension (50% in mineral oil), 15 g., was washed with hexane and added in portions to a solution of 36 g. of **3c** in 400 ml. of dimethylformamide. After complete addition, the mixture was heated to reflux for 10 minutes with stirring under nitrogen. The cooled solution was then poured into 2 l. of ice water. The precipitate was collected, washed with water and recrystallized from boiling dimethylformamide to yield 29.6 g. (87%) of product with m.p. 295-298°; ir (potassium bromide): 3250 cm^{-1} (NH) 1640 (C=O).

Anal. Calcd. for $C_{19}H_{18}ClN_3O$: C, 67.1; H, 5.3; N, 12.4. Found: C, 67.0; H, 5.3; N, 12.6.

10-Chloro-5-(2-dimethylaminoethyl)-7-methyl-7*H*-indolo[2,3-*c*]-quinolin-6(5*H*)one (**5d**).

A mixture of 37.4 g. (0.1 mole) of **3d**, 7.5 g. (0.15 mole) of sodium hydride suspension (50% in mineral oil) and 200 ml. of dimethylformamide was heated to reflux for 10 minutes. The product was precipitated by addition of water, was collected, washed with water and dissolved in methylene chloride. The solution was dried and evaporated. Crystallization of the residue from benzene/hexane gave 31.7 g. (89%) with m.p. 150-152°; uv: λ max 221 mμ (ε, 29,100), 240 (33,100), 253 (38,700), 251 (40,900), 278 (22,750), 289 (7,600), 300 (9,700), 314 (11,300), 350 (13,100), 367 (13,400).

Anal. Calcd. for $C_{20}H_{20}ClN_3O$: C, 67.9; H, 5.7; N, 11.9. Found: C, 67.9; H, 5.6; N, 11.9.

10-Chloro-5-dimethylamino-7*H*-indolo[2,3-*c*]quinolin-6(5*H*)one (**5e**).

A mixture of 12.5 g. of **3e**, 5 g. of sodium hydride suspension and 200 ml. of dimethylformamide was heated to reflux for 10 minutes. The usual workup followed by crystallization from chloroform/methanol yielded 9.4 g. (80%) of colorless product with m.p. 311-313°. For analysis it was recrystallized from chloroform/ethanol, m.p. 313-315°; uv: λ max 220 mμ (ε, 26,600) 238 (32,950), 251 (42,300), 258 (42,500), 274 (20,000), 299 (9,000), 312 (12,500), 326 (8,000), 340 (11,700), 356 (11,400).

Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.43; H, 4.60; N, 13.46.

5-Chloro-3-(2-fluorophenyl)-1-methylindole-2-carboxaldoxime (**6**).

A mixture of 5.8 g. of **4**, 2.8 g. of hydroxylamine hydrochloride, 3.2 g. of sodium acetate and 75 ml. of ethanol was refluxed for 1 hour. The crystals which separated upon dilution with water, were collected, washed with water and dried, yield 5.6 g. (91%). The analytical sample was recrystallized from ethanol, m.p. 193-195°.

Anal. Calcd. for $C_{16}H_{12}ClFN_2O$: C, 63.5; H, 4.0; N, 9.3. Found: C, 63.7; H, 4.0; N, 9.3.

2-Acetyl-3-(2-fluorophenyl)indole (**7**).

A mixture of 47.6 g. of ethyl 2-acetyl-3-(2-fluorophenyl)-propionate, 75 ml. of ethanol, 300 ml. of water and 9 g. of sodium hydroxide was stirred at room temperature for 3 hours. A diazonium salt solution prepared from 18 g. of aniline, 50 ml. of concentrated hydrochloric acid, 50 ml. of water and 13 g. of sodium nitrite was then added to the mixture. After the addition of 30 g. of sodium acetate in portions, stirring was continued for 1 hour at room temperature. The precipitated material was collected, washed with water and refluxed for 4 hours in 100 ml. of ethanol and 100 ml. of concentrated hydrochloric acid. The separated crystals were filtered, washed with water and ethanol. Recrystallizations from acetone/hexane and from ethanol yielded 21 g. (41%) of product with m.p. 152-154°; uv: λ max 224 mμ (ε, 17,800), infl 238 (16,000), 243 (16,300), 313 (19,500); ir (chloroform): 3450 cm^{-1}, 3350 (NH), 1650 (C=O); nmr (deuteriochloroform): δ 2.23 ppm (s, 3, $COCH_3$), 7-7.8 (m, 8, aromatic H) 9.6 (broad s, 1, NH).

Anal. Calcd. for $C_{16}H_{12}FNO$: C, 75.9; H, 4.8; N, 5.5. Found: C, 75.9; H, 4.8; N, 5.6.

10-Chloro-7-methyl-7*H*-indolo[2,3-*c*]quinoline 5-Oxide (**8a**).

A mixture of 3 g. of **6**, 50 ml. of ethanol and 1.4 ml. of 40% aqueous sodium hydroxide was refluxed for 2 days. The yellow crystals which separated were collected, washed with water and ethanol to leave 1.9 g. (67%) of product with m.p. 297-299° dec., after recrystallization from dimethylformamide; uv: λ max 226 mμ (ε, 20,800), infl 245 (23,500), 261 (35,200), infl 295 (6,500), 300 (3,550), 370 (22,000), sh 410 (6,800).

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: C, 68.0; H, 3.9; N, 9.9. Found: C, 68.1; H, 3.8; N, 9.9.

6-Methyl-7*H*-indolo[2,3-*c*]quinoline 5-Oxide (**8b**).

A mixture of 12.5 g. of **7**, 7 g. of hydroxylamine hydrochloride, 8 g. of sodium acetate and 125 ml. of ethanol was refluxed for 1 hour. After dilution with water, the oxime was extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from methanol/water yielded 12 g. of oxime which was refluxed for 3 days in 150 ml. of ethanol and 10 ml. of 40% aqueous sodium hydroxide. The separated crystals were collected, washed with water and methanol and dried to leave 7 g. (56%) of product. The yellowish crystals obtained by recrystallization from benzene/methanol had m.p. 305-306°; uv: λ infl 219 mμ (ε, 15,000), infl 235 (20,800), max 253 (34,750), 267 (36,750), 289 (7,500), 301 (6,200), 355 (21,300), 371 (19,750), infl 390 (9,750).

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.4; H, 4.9; N, 11.3. Found: C, 77.4; H, 4.7; N, 11.4.

11-Chloro-1,2,3,4,14,14b-hexahydro-14-methylindolo[2,3-*c*]-pyrimido[1,2-*a*]quinoline (**9**).

A mixture of 14.4 g. (0.05 mole) of **4** and 50 ml. of 1,3-diaminopropane was refluxed for 1 hour with distillation of 21 ml. of the reagent. The cool reaction mixture was then partitioned between methylene chloride and water. The organic layer was washed with water, dried and evaporated. Crystallization of the residue from methylene chloride/ether yielded 14.2 g. (87%) of product with m.p. 190-193°. For analysis it was recrystallized from methylene chloride/hexane, m.p. 195-197°; uv: λ max 237 mμ (ε, 34,900), 271 (19,900), infl 286 (13,500), 327 (8,800), infl 370 (3,200), 433 (360); nmr (deuteriochloroform): δ 1.37 ppm (broad s, 1, NH) *ca.* 1.6 (m, 2, C-CH_2-C) 3-3.5 (m, 3, N-CH_2) 3.62 (s, 3, N-CH_3) 4.25 (broad d, 1, J = 14 Hz, -N-CH_2-) 5.5 (s, 1, C 14b -H) 6.7-8.2 (m, 7, aromatic H); ms: m/e 323 (M+) 322, 321, 320, 307, 293, 280, 266.

Anal. Calcd. for $C_{19}H_{18}ClN_3$: C, 70.5; H, 5.6; N, 13.0. Found: C, 70.5; H, 5.5; N, 13.0.

10-Chloro-1,2,3,13b-tetrahydro-1,13-dimethyl-13*H*-imidazo[1,2-*a*]-indolo[2,3-*c*]quinoline (**10b**).

A mixture of 5.8 g. (0.02 mole) of **4** and 15 ml. of 2-methylaminoethylamine was refluxed for 3 hours with distillation of 4 ml. of the amine. The cooled reaction mixture was partitioned between water and methylene chloride. The organic layer was washed with water, dried and evaporated. Crystallization of the residue from methylene chloride/ether yielded 3.5 g. (54%) of pale yellow crystals with m.p. 208-212° after recrystallization from benzene/ethanol: uv: λ max 231 mμ (ε, 33,500), infl 243 (28,400), 270 (25,900), infl 286 (12,600), infl 325 (6,900), 351 (10,250), 362 (10,000), *ca.* 430 (2,200); nmr (deuteriochloroform): δ 1.93 ppm (s, 3, N-CH_3) 2.9-3.6 (m, 4, -CH_2CH_2-) 3.57 (s, 3, N-CH_3) 5.65 (s, 1, C 13b -H) 6.4-8.2 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{18}ClN_3$: C, 70.5; H, 5.6; N, 13.00. Found: C, 70.6; H, 5.7; N, 13.1.

11-Chloro-2,3,4,14-tetrahydro-14-methylindolo[2,3-*c*]pyrimido-[1,2-*a*]quinoline (**11**).

A mixture of 6.5 g. (0.02 mole) of **9**, 300 ml. of benzene and 20 g. of manganese dioxide was refluxed for 10 minutes. The manganese dioxide was filtered off and the filtrate was evaporated. Crystallization of the residue from methylene chloride/ethanol yielded 5.85 g. (91%) of light yellow prisms with m.p. 192-194°. A lower melting crystal modification, needles, with m.p. 182-183°, was also observed; uv: λ infl 230 mμ (ε, 32,400), max 248 (52,250), 262 (35,200), infl 283 (16,300) 245 (18,600), 312 (9,800), 327 (7,500), 340 (9,100), 356 (14,300), 374 (13,000); nmr (deuteriochloroform): δ 2.01 ppm (m, 2, -CH_2-) 3.68 (m, 4, N-CH_2) 3.87 (s, 3, N-CH_3) 6.9-7.3 and 7.8-8.1 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{16}ClN_3$: C, 70.9; H, 5.0; N, 13.1. Found: C, 70.7; H, 5.0; N, 13.1.

10-Chloro-2,3-dihydro-13-methyl-13*H*-imidazo[1,2-*a*]indolo-[2,3-*c*]quinoline (**12**).

A mixture of 20 g. (0.07 mole) of **4** and 75 ml. of ethylenediamine was refluxed for 3 hours with distillation of 30 ml. of solvent. After cooling, the reaction mixture was diluted with ethanol and water. The separated crystals were collected and washed with water, ethanol and ether to leave 14.5 g. of product which according to thin layer chromatogram was a mixture of 10-chloro-1,2,3,13b-tetrahydro-13-methyl-13*H*-imidazo[1,2-*a*]-indolo[2,3-*c*]quinoline (**10a**) and the oxidized product **12**. This mixture was stirred with 45 g. of manganese dioxide and 1 l. of methylene chloride for 1 hour at room temperature. The residue obtained after filtration and evaporation was crystallized from methylene chloride/ethanol to yield 13 g. (60%) of light yellow crystals with m.p. 220-222°. For analysis it was recrystallized from ethanol/benzene; uv: λ max 249 mμ (ε, 47,100), 298

(14,750), 315 (6,820), 331 (4,800), 353 (7,250), 370 (9,980), 390 (7,650); nmr (deuteriochloroform): δ 3.95 ppm (s, 3, N-CH_3), 3.4-4.35 (m, 4, -CH_2-CH_2-), 6.5-8 (m, 7, aromatic H); ms: m/e 307 (M^+), 306, 291, 279, 153.5 (M^{++}).

Anal. Calcd. for $C_{18}H_{14}ClN_3$: C, 70.3; H, 4.6; N, 13.7. Found: C, 70.1; H, 4.3; N, 13.8.

10-Chloro-13-methyl-13*H*-imidazo[1,2-*a*]indolo[2,3-*c*]quinoline (**13**).

A mixture of 6.16 g. (0.02 mole) of **12**, 500 ml. of toluene and 20 g. of manganese dioxide was refluxed for 1 hour. The manganese dioxide was filtered off and washed well with methylene chloride. The filtrate was evaporated and the residue was crystallized from methylene chloride/ethanol to yield 5.5 g. (90%) of product with m.p. 218-220°; uv: λ max 216 mμ (ε, 20,500), infl 224 (17,900), 240 (30,000), infl 265 (37,000), 272 (50,000), infl 294 (17,500), infl 311 (9,000), 327 (16,500), 341 (22,700), 359 (19,500); nmr (deuteriochloroform): δ 4.2 ppm (s, 3, N-CH_3) 7.2-8.2 (m, 9, aromatic H); ms: m/e 305 (M^+).

Anal. Calcd. for $C_{18}H_{12}ClN_3$: C, 70.7; H, 4.0; N, 13.7. Found: C, 70.6; H, 3.9; N, 13.8.

5-Chloro-2-cyanomethyl-3-(2-fluorophenyl)-1-methylindole (**14**).

A mixture of 20 g. of **2**, 200 ml. of methylene chloride and 10 ml. of phosphorus tribromide was stirred at room temperature for 3 hours. This reaction mixture was poured slowly into a stirred mixture of 200 ml. of dimethylformamide, 100 ml. of 10% aqueous sodiumcarbonate and 30 g. of potassium cyanide. The methylene chloride was distilled from the reaction mixture by gradually heating it to 80°. The product was crystallized by addition of water and cooling in ice. It was collected and recrystallized from methanol to yield 14.4 g. (69%) of product with m.p. 142-144°; uv: λ max 228 mμ (ε, 40,100), 280 (11,000); nmr (deuteriochloroform): δ 3.82 ppm (s, 2, -CH_2-CN) 3.86 (s, 3, N-CH_3) 7.1-7.7 (m, 7, aromatic H).

Anal. Calcd. for $C_{17}H_{12}ClFN_2$: C, 68.3; H, 4.0; N, 9.4. Found: C, 68.4; H, 4.0; N, 9.2.

2-(2-Aminoethyl)-5-chloro-3-(2-fluorophenyl)-1-methylindole Hydrochloride (**15**).

Compound **14**, 13 g. was added to a suspension of 4 g. of lithium aluminum hydride in 200 ml. of ether. Following the addition, the mixture was heated to reflux for 3 hours and then hydrolysed by careful addition of 20 ml. of water. The inorganic material was separated and washed well with methylene chloride. The filtrate was dried and evaporated. The residue was dissolved in ether and ethanolic hydrogen chloride was added to the solution. The crystalline hydrochloride, 7.9 g. (58%) was recrystallized from ethanol/ether for analysis, m.p. 268-270°; uv: λ max 231 mμ (ε, 38,800), 284 (10,500).

Anal. Calcd. for $C_{17}H_{16}ClFN_2HCl$: C, 60.2; H, 5.0; N, 8.3. Found: C, 60.1; H, 4.9; N, 8.2.

11-Chloro-5,8-dihydro-5,8-dimethylindolo[2,3-*d*] [1]benzazepine (**16**).

A mixture of 5 g. of **15**, 50 ml. of dimethylformamide and 3 g. of sodium hydride suspension (50% in mineral oil) which had been washed oil-free with hexane was stirred and heated to reflux for 30 minutes under nitrogen atmosphere. The cooled reaction mixture was diluted with water and extracted with benzene. The benzene extracts were washed with water, dried and evaporated. The residue was chromatographed over 80 g. of silica gel using 25% methylene chloride in hexane. Crystallization of the combined clean fractions from ethanol yielded 0.54 g. (12.5%) of orange needles with m.p. 161-163°; uv: λ max 229 mμ (ε, 24,600), 250 (26,000), sh 266 (20,750), 279 (20,600), 304 (12,200), infl 370 (2,600); nmr (deuteriochloroform): δ 3.05 ppm (s, 3, N-CH_3), 3.68 (s, 3, N-CH_3), 5.77 (d, 1) and 6.05 (d, 1) (AB-system, J = 8 HZ, -CH=CH-), 6.8-7.9 (m, 7, aromatic H); MS: m/e 294 (M^+), 279, 264.

Anal. Calcd. for $C_{18}H_{15}ClN_2$: C, 73.3; H, 5.1; N, 9.5. Found: C, 73.1; H, 5.1; N, 9.4.

2'-Cyano-2-(2-fluorophenyl)acetanilide (**18a**).

A mixture of 50 g. of 2-fluorophenyl acetic acid and 150 ml. of thionyl chloride was refluxed for 1 hour. The reagent was removed under reduced pressure at the end azeotropically with benzene. The liquid residue was dissolved in 300 ml. of dimethylformamide containing 42 g. of anthranilonitrile. Seventeen g. of sodium hydride suspension (50% in mineral oil) was washed with hexane and was added in portions to the mixture cooled with an ice bath. After complete addition, the reaction mixture was poured into ice/water and was neutralized by dilute acetic acid. The precipitated product was collected and dissolved in methylene chloride. The methylene chloride solution was dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride/hexane yielded 43.6 g. (49%) of product with m.p. 168-170°; ir (chloroform): 3410, 3385 cm^{-1} (NH), 2225 (CN), 1720 (CO).

Anal. Calcd. for $C_{15}H_{11}FN_2O$: C, 70.9; H, 4.4; N, 11.0. Found: C, 70.8; H, 4.3; N, 11.0.

Methyl *N*-(2-Fluorophenylacetyl)anthranilate (**18b**).

Fluorophenylacetyl chloride was prepared as described in the previous example from 85 g. of 2-fluorophenyl acetic acid and 250 ml. of thionyl chloride. Reaction with 90 g. of methyl anthranilate and 32 g. of sodium hydride suspension yielded after the same workup and after recrystallizations from methanol/-water and methylene chloride/hexane, 89 g. (52%) of product with m.p. 78-80°.

The analytical sample was recrystallized from methylene chloride/hexane, m.p. 80-83°; ir (chloroform): 3300 cm^{-1} (NH), 1680/90 NCO, $COOCH_3$); nmr (deuteriochloroform): 3.82 ppm (s, 2, CH_2), 3.85 (s, 3, OCH_3), 6.7-8.1 (m, 7, aromatic H), 8.7 (d, J = 8 Hz, 1, aromatic H), 11.1 (broad s, 1, NH).

Anal. Calcd. for $C_{16}H_{14}FNO_3$: C, 66.9; H, 4.9; N, 4.9. Found: C, 67.1; H, 4.9; N, 4.8.

3-(2-Fluorophenyl)-4-hydroxyquinolin-2(1*H*)one (**20a**).

Sodium hydride suspension, 13 g. was washed with hexane and added in portions to a solution of 13.3 g. of **18b** in 150 ml. of dimethylformamide, kept at 60 to 70°. After stirring under nitrogen for 2 hours, the reaction mixture was poured into ice/-water and acidified with acetic acid. The precipitated product was collected, washed with water and recrystallized from aqueous dimethylformamide to yield 7.9 g. (60%) with m.p. 330-335° dec.; uv: λ max 231 mμ (ε, 43,800), 281 (10,400), 320 (8,400); ir (potassium bromide): 3300-2500 cm^{-1} (NH, OH), 1640 (CO).

Anal. Calcd. for $C_{15}H_{10}FNO_2$: C, 70.6; H, 3.9; N, 5.5. Found: C, 70.3; H, 4.0; N, 5.5.

4-Amino-3-(2-fluorophenyl)quinolin-2(1*H*)one (**20b**).

Sodium hydride suspension, 10 g. (50% in mineral oil) was washed with hexane and was added in portions to a solution of 10.6 g. of **18a** in 200 ml. of dimethylformamide. The mixture was stirred under nitrogen for 4 hours at 60 to 70°. It was poured on ice/water and the precipitate was collected, washed with water

and dried. Recrystallization with methylene chloride/methanol yielded 7 g. (66%) of product with m.p. 313-315°; uv: λ max 224 mμ (ε, 42,000); infl 244 (19,000), 303 (10,250), sh 315 (9,500), infl 332 (6,250); ir (potassium bromide): 3470, 3330 cm^{-1} (NH), 1640 (C=O); nmr (DMF) δ 6.25 ppm (s, 2, NH_2), 7-8.3 (m, 8, aromatic H), 11.30 (s, 1, NH).

Anal. Calcd. for $C_{15}H_{11}FN_2O$: C, 70.9; H, 4.4; N, 11.0. Found: C, 70.9; H, 4.3; N, 11.1.

2-Chlorobenzofurano[2,3-*c*]quinolin-6(5*H*)one (**21a**).

Sodium hydride suspension 2.4 g. (50% in mineral oil) was washed with hexane and added to a solution of 5.8 g. of 7-chloro-1,2-dihydro-4-(2-fluorophenyl)-3-hydroxy-2-oxoquinoline (8) in 60 ml. of dimethylformamide. The mixture was stirred and refluxed for 5 hours in an atmosphere of nitrogen. The product was precipitated by addition of water to the cooled reaction mixture. The crystals were collected, washed with water, methanol and ether to leave 4.7 g. (87%) with m.p. >360°. The analytical sample was recrystallized from dimethylformamide; uv: λ max (2-PrOH + 10% DMF), 248 mμ (ε, 22,400), 268 (9,820), 284 (10,320), 292 (12,500), infl 317 (6,820), 329 (9,380), 344 (7,200); ir (potassium bromide): 3125 cm^{-1} NH, 1650/1670 cm^{-1} (C=O); MS: m/e 269 (M^+), 240, 206, 177, 134.5 (M^{2+}).

2-Chloro-5-(2-diethylaminoethyl)benzofurano[2,3-*c*]quinolin-6-(5*H*)one (**21b**).

Sodium hydride suspension, 1 g., was washed with hexane and added to a solution of 2.7 g. of **21a** in 100 ml. of hot dimethylformamide. After the evolution of hydrogen had ceased, 10 ml. of a 40% solution of 2-diethylaminoethyl chloride in benzene was added. The mixture was stirred for 30 minutes at 70 to 80°, was poured into water and extracted with benzene. The extracts were dried and evaporated. Crystallization of the residue from ethanol yielded 3.2 g. (86%) of product with m.p. 178-180°, after two recrystallizations from ethanol; uv: λ max 237 mμ (ε, 58,700), 268 (9,650), sh 278 (9,050), 290 (12,000) 301 (14,350), infl 321 (7,600), 333 (9,500), infl 347 (7,400); ir (chloroform): 1660 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.08 ppm (t, 6, CH_3), 2.5-3.1 (m, 6, N-CH_2), 4.55 (t, 2, N-CH_2) 7.3-8.4 (m, 7, aromatic H).

Anal. Calcd. for $C_{21}H_{21}ClN_2O_2$: C, 68.4; H, 5.7; N, 7.6. Found: C, 68.3; H, 5.5; N, 7.4.

A small amount of the *o*-alkylated product, 2-chloro-6-(2-diethylaminoethoxy)benzofurano[2,3-*c*]quinoline (**23**) was isolated from the original mother liquor by fractional crystallization, m.p. 90-91°; uv: λ max 239 mμ (ε, 60,500), infl 253 (18,000), 262 (11,400), infl 282 (8,000), 296 (13,800), 304 (15,700), 319 (11,100), infl 325 (7,250), 334 (14,500); ir (chloroform): no CO absorption; nmr (deuteriochloroform): δ 1.14 ppm (t, 6, CH_3), 2.7 (q, 4, N-CH_2), 3.04 (t, 2, N-CH_2), 4.76 (t, 2, OCH_2), 7.3-8.5 (m, 7, aromatic H).

Anal. Calcd. for $C_{21}H_{21}ClN_2O_2$: C, 68.4; H, 5.7; N, 7.6. Found: C, 68.5; H, 5.9; N, 7.4.

Benzofurano[3,2-*c*]quinolin-6(5*H*)one (**22a**).

Sodium hydride suspension, 36 g., (50% in mineral oil) was washed with hexane and added in portions to a solution of 58 g. of **18b** in 750 ml. of dimethylformamide heated to 100-120°. After complete addition, the temperature was slowly raised to reflux the solvent. The reaction mixture was refluxed for 1 hour with stirring under nitrogen, then cooled and poured into ice/water. The solid precipitate was collected and washed with water and methanol. Recrystallization from aqueous dimethylformamide yielded 26 g. (55%) of product with m.p. 310-315°. The analytical sample was sublimed under high vacuum; uv: λ max 237 mμ (ε, 51,000), 258 (12,200) infl 276 (7,600) infl 285 (11,750), 288 (12,800), infl 284 (11,500), 299 (23,200), infl 317 (10,000), 329 (16,200), 345 (16,700); ir (potassium bromide); 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_9NO_2$: C, 76.6; H, 3.9; N, 6.0. Found: C, 76.5; H, 3.8; N, 5.9.

5,11-Dihydro-6*H*-indolo[3,2-*c*]quinolin-6-one (**22b**) (**5b**).

Sodium hydride suspension, 30 g., (0.625 mole) was washed with hexane and added in portions to a solution of 33 g. (0.13 mole) of **18a** in 500 ml. of dimethylformamide. During the addition, the temperature was kept at 90 to 110° and was then raised to 140-150° for 1 hour with stirring under nitrogen. The cooled mixture was poured into ice/water and the precipitated product was collected, washed with water, methanol and ether. Recrystallization from a large volume of methylene chloride/-methanol yielded 16.2 g. (53%) of product with m.p. > 350°.

Anal. Calcd. for $C_{15}H_{10}N_2O$: C, 76.9; H, 4.3; N, 12.0. Found: C, 77.0; H, 4.5; N, 11.9.

The spectral data are in agreement with those reported by Winterfeldt (5b).

5-(2-Diethylaminoethyl)benzofurano[3,2-*c*]quinolin-6(5*H*)one (**22c**).

Sodium hydride suspension, 7.5 g., (0.155 mole) (50% in mineral oil) was washed with hexane and added to a solution of 21 g. (0.09 mole) of **20a** in 200 ml. of warm dimethylformamide. After the hydrogen evolution had subsided, 42 ml. of a 44% solution of 2-diethylaminoethyl chloride in toluene was added. The mixture was stirred overnight at room temperature and then poured into water. The precipitated oil, which slowly solidified, was collected, washed with water and dissolved in methylene chloride. The solution was dried and evaporated. Crystallization from methylene chloride/hexane yielded 18.7 g. (62%) of product with m.p. 101-104°. The analytical sample was recrystallized from the same solvent mixture, m.p. 104-106°; uv: λ max 238 mμ (ε, 47,000), 258 (15,500), 291 (13,900), 301 (18,700), 330 (15,000), 346 (15,500); ir (chloroform): 1660 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.1 ppm (t, 6, CH_3), 2.76 (t, 4, CH_2), 2.82 (t, 2, CH_2), 4.5 (t, 2, CH_2), 7.2-8.5 (m, 8, aromatic H).

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.4; H, 6.6; N, 8.4. Found: C, 75.4; H, 6.5; N, 8.4.

The mother liquor was concentrated to an oil which was subjected to chromatography on silica gel. By elution with 10% ethanol in ethyl acetate, 1.05 g. (3.5%) of *o*-alkylated product, 6-(2-diethylaminoethoxy)benzofurano[3,2-*c*]quinoline (**24**) was obtained. The analytical sample was recrystallized from petroleum ether, m.p. 57-59°; uv: λ max 246 mμ (ε, 54,500), 254 (51,750), 274 (13,200), 286 (17,450), 296 (24,400), 315 (7,000), 329 (8,600).

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.4; H, 6.6; N, 8.4. Found: C, 75.1; H, 6.7; N, 8.3.

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