work and the National Science Foundation for Research Equipment Grant GP3618 that provided funds for the purchase of a Varian A-60 nmr spectrometer. Also, we wish to acknowledge the kind cooperation of Dr. J. M. Bobbitt in informing us of his work before publication and of Mr. D. W. Smith, Monsanto Chemical Company, Everett, Mass., for taking some of the nmr spectra.

# Acylindoles. I. The Synthesis and Transformations of 3-(2-Aminobenzoyl)indoles

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The acid-catalyzed rearrangement of appropriately substituted 3-(2-aminobenzoyl)indoles and 5-(3-indolyl)-2,3-dihydro-1,4-benzodiazepines was found to result in the formation of indolo[3,2-*c*]quinolines, 3-(2-aminophenyl)-4(1H)-quinolones, and an imidazo[1,2-*a*]indolo[3,2-*c*]quinoline. An independent synthesis of the 3-(2-aminophenyl)-4(1H)-quinolones is described. The requisite indolylbenzodiazepines were prepared from the corresponding 3-(2-fluorobenzoyl)indoles by treatment with ethylenediamine.

The synthesis of heterocyclic systems such as dibenzodiazocines,[1] quinazolines,[2] benzodiazepines,[3] indoles,[4] and quinolones[5] from aromatic *o*-amino ketones has now been well established, and consequently we have investigated the synthesis and subsequent transformations of some 3-(2-aminobenzoyl)indoles. While these compounds can be utilized as starting materials for the synthesis of other heterocyclic moieties, we have found that these indoles readily undergo acid-catalyzed rearrangements to give quinolones and indoloquinolines.

The preparation of the aminobenzoylindoles was effected by a nucleophilic exchange of fluorine for amines on 3-(2-fluorobenzoyl)indole (**1**)[6] (Scheme I). Compound **1** was obtained by the acylation of indolylmagnesium bromide with *o*-fluorobenzoyl chloride. Also isolated from this reaction was 1,3-di(2-fluorobenzoyl)indole which was readily converted into **1** by treatment with aqueous alkali. A Vilsmeier type of reaction carried out as described by Anthony,[7] for the synthesis of 3-benzoylindole was also utilized, but the yield of **1** was, in this instance, much lower than that obtained from the Grignard reaction. Alkylation of **1** with dimethyl sulfate in the presence of sodium hydroxide afforded the N-methyl derivative **2**.

Treatment of **1** with ethylenediamine gave the corresponding indolylbenzodiazepine **3**, while the amination of **2** with benzylamine gave the substituted aminobenzoylindole **4**. Treatment of these acyl- or iminoindoles with acid resulted in both cases in rearrangement. Thus, compound **4** when treated with hot aqueous acid afforded a mixture of the quinolone **5** and the indoloquinoline **6**.[8] Under somewhat similar conditions, compound **3** gave the corresponding quinolone **7**.

More energetic treatment of **3** with acid gave the indoloquinoline **8**, which could also be obtained from compound **7** under similar conditions. By heating **7**, in high-boiling solvents, either the previously described indoloquinoline **9**[9] or a mixture of **9** and the dealkylated quinolone **10** was obtained. Thus, by heating a solution of **7** in diphenyl ether under reflux, compound **9** was the only detectable product, while in nitrobenzene both **9** and **10** were obtained.

The mechanism of the rearrangement of **4** to the quinolone **5** can be explained by the initial protonation of **4** at the carbonyl oxygen[10] to give the indolenine intermediate A (Scheme II). Nucleophilic addition of the anilino N–H function to the polarized C=N bond of A, as shown, followed by hydrolytic cleavage of the resultant intermediate B at the C–N bond of the five-membered ring would then lead directly to the observed quinolone **5**.

Evidence that the mechanism for the conversion of **3** into **7** is similar and initially involves the hydrolytic cleavage of the azomethine bond was given by the observation that base cleavage of the 4-methyl quaternary salt of **3** (compound **11**) gave the corresponding methylaminoethylaminoindole **12**, which when subjected to hot mineral acid, underwent a similar rearrangement to give a 60% yield of the quinolone **13** (Scheme III). A minor product isolated from the reaction mixture was the indoloquinoline **14**, isolated as the dihydrochloride hemihydrate. The formation of the indoloquinolines from the intermediate quinolones is self-explanatory and would involve condensation of the anilino amine with the quinolone carbonyl group.

The proof of structure for the quinolones **5**, **7**, and **10** was given by the following unequivocal syntheses. Ethyl 2-nitrophenylacetate upon treatment with N,N-dimethylformamide diethyl acetal[11] afforded the aminoacrylate **15**. This was not isolated but was directly converted by acid treatment into the acrylate **16**[12] (Scheme IV).

(1) W. Metlesics, T. Resnick, G. Silverman, R. Tavares, and L. H. Sternbach, *J. Med. Chem.*, **9**, 633 (1966).

(2) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 3957 (1965).

(3) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

(4) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *ibid.*, **32**, 3798 (1967).

(5) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964).

(6) The susceptibility of a fluorine *ortho* to a carbonyl group toward nucleophilic exchange with amines has previously been demonstrated by R. I. Fryer, J. V. Earley, and L. H. Sternbach, *ibid.*, 4979 (1963). See also H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).

(7) W. C. Anthony, *ibid.*, **25**, 2049 (1960).

(8) For convenience and simplicity, the compounds described throughout the discussion will be referred to by number or letter corresponding to their correct structures.

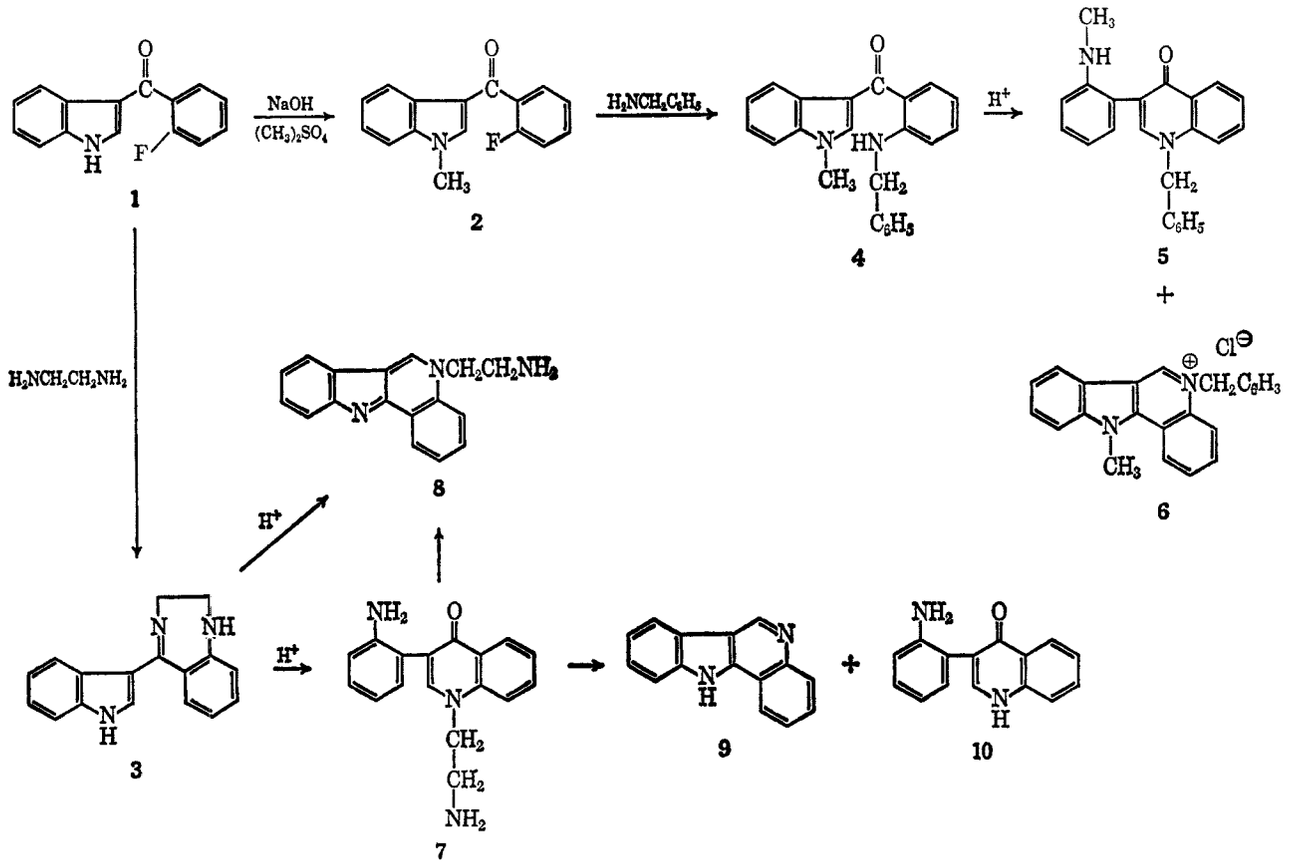
(9) W. O. Kermack and N. E. Storey, *J. Chem. Soc.*, 607 (1950).

(10) R. L. Hinman and E. B. Whipple [*J. Amer. Chem. Soc.*, **84**, 2534 (1962)] have established that the principal conjugate acid of indole in strong acid is the 3-protonated isomer. The 3-acylindoles have been found to protonate primarily at the acyl oxygen [G. Berti and A. da Settimo, *Gazz. Chim. Ital.*, **91**, 728 (1961)].

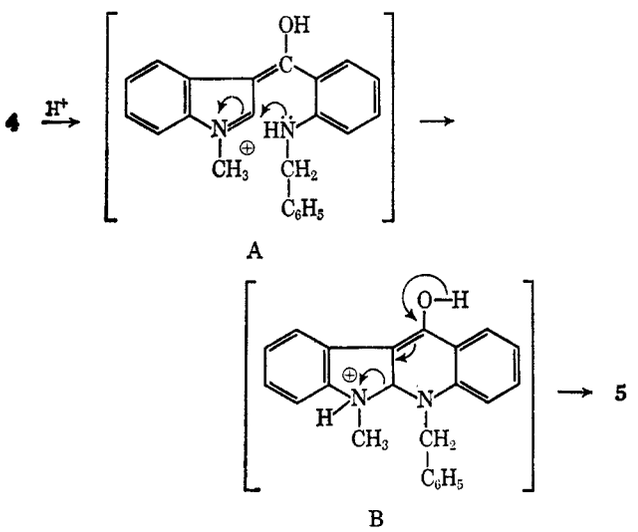
(11) H. Meerwein, *Angew. Chem.*, **71**, 530 (1959).

(12) Formylation of ethyl 2-nitrophenylacetate with sodium and ethyl formate was unsuccessful.

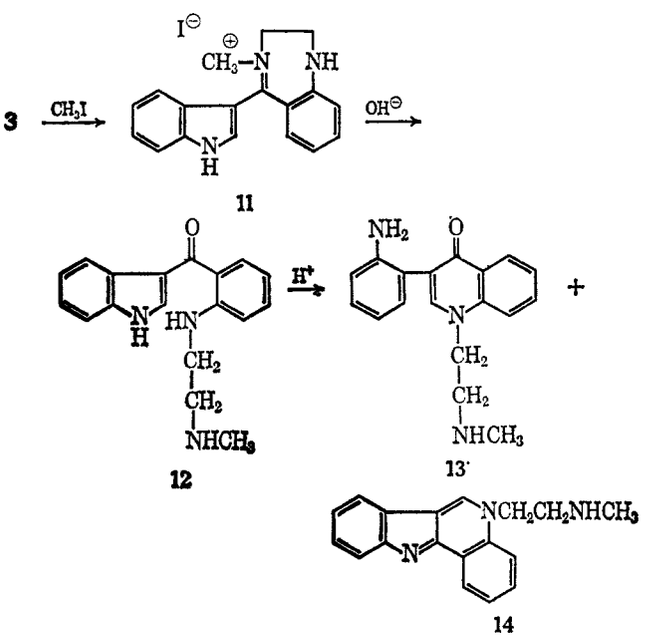
SCHEME I



SCHEME II



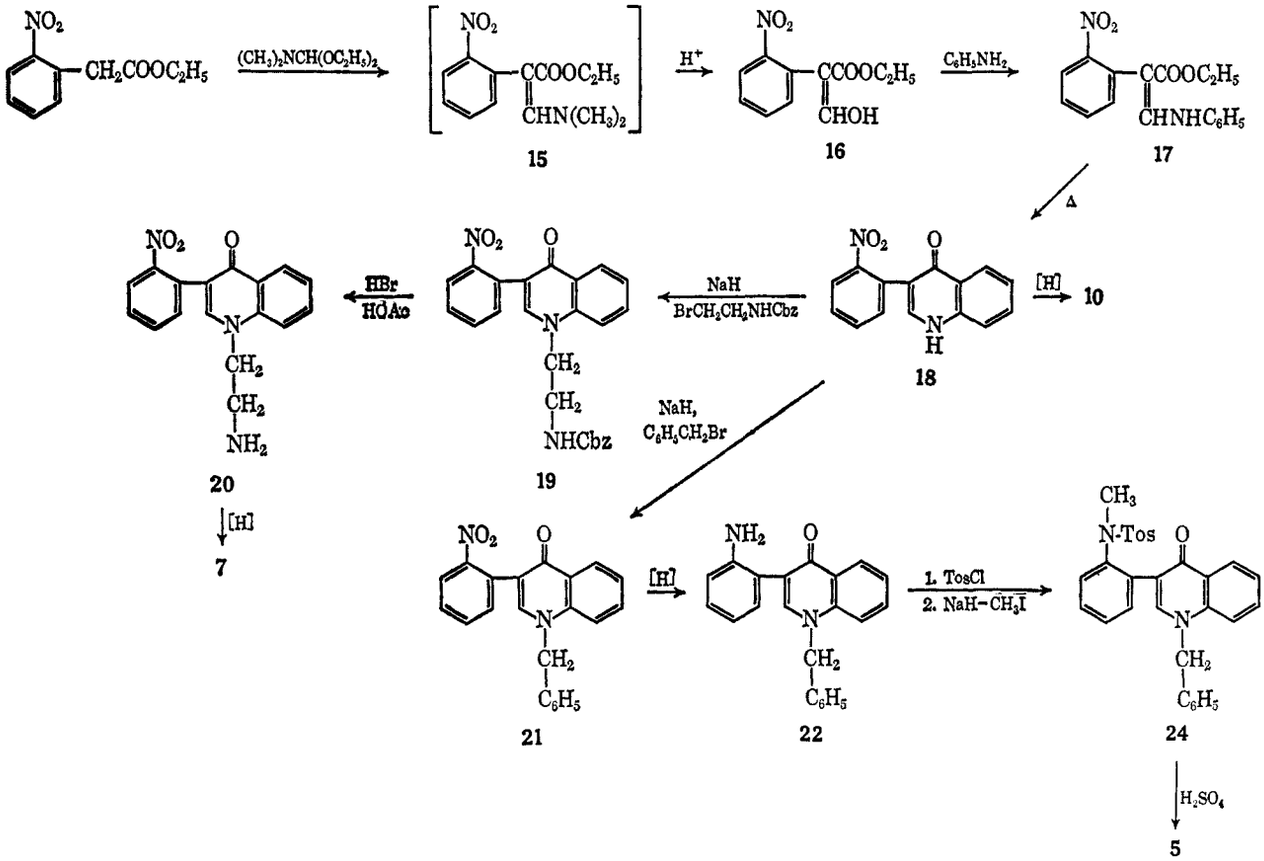
SCHEME III



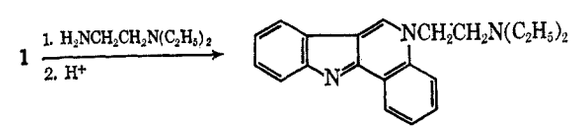
Treatment of **16** with aniline gave **17** as a mixture of *cis* and *trans* isomers. The isomers were not characterized and, in general, were not separated since both could be cyclized by heating under reflux in diphenyl ether to give the desired quinolone (compound **18**). Catalytic reduction of the nitro group gave an authentic sample of the corresponding aminoquinolone **10** which was identical in all respects with the substance obtained by subjecting **7** to prolonged heating in nitrobenzene. Treatment of **18** with sodium hydride followed by the addition of carbobenzoxy-2-bromoethylamine gave compound **19**. Cleavage of the carbobenzoxy group with hydrogen bromide in acetic acid gave the free amino derivative **20**. Reduction of **20** then gave an authentic sample of **7** which was identical with the product obtained by acid-catalyzed rearrangement of **3**. By forming the N-benzyl derivative of **18** (compound **21**), carrying out the reduction and alkylation steps as shown in Scheme IV, an authentic sample of **5** was also obtained.

The structure of the indoloquinoline **9** was confirmed by a comparison with an authentic sample.[9] The structures of the substituted indoloquinolines **8** and **14**

SCHEME IV



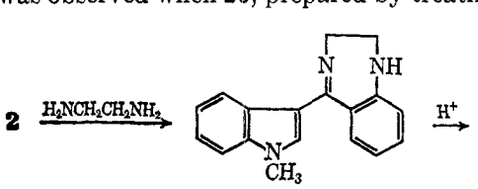
were assigned primarily on the basis of compatible physical data. However, both compounds have ultraviolet spectra almost superimposable on that of the previously described N,N-diethylaminoethyl derivative, compound **25**.[9] Furthermore, treatment of compound **1** with N,N-diethylethylenediamine followed by acid-catalyzed rearrangement of the product gave compound **25** which was then converted into the dimethiodide and



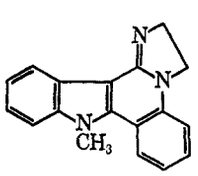
**25**

was compared with and shown to be identical with an authentic sample.[9] Compound **6** upon heating at reduced pressure readily underwent debenzylation to yield 11-methyl-11H-indolo[3,2-*c*]quinoline.[13]

An analogous rearrangement of an indolodiazepine was observed when **26**, prepared by treatment of **2** with



**26**



**27**

ethylenediamine, was subjected to acid hydrolysis. In this instance the imidazoindoloquinoline **27** was the only product isolated. The assignment of the imidazoindoloquinoline structure follows by analogy and also from consistent spectral data. For example, the mass spectrum showed the parent ion at *m/e* 273, compatible with structure **27**, in addition to the strong loss of one and two hydrogens (*m/e* 272 and 271). Also in accord with structure **27** were the infrared and nmr spectra which were completely devoid of any N–H absorption.

## Experimental Section[14]

**3-(2-Fluorobenzoyl)indole (1). A. From *o*-Fluoro-N,N-dimethylbenzamide, Indole, and Phosphorus Oxychloride.**—A solution of 15.9 g (0.135 mol) of indole, 44.8 g (0.268 mol) of *o*-fluoro-N,N-dimethylbenzamide, and 15 ml of $POCl_3$ was heated with vigorous stirring. After reaching 88° a vigorous exothermic reaction occurred and ice-bath cooling was applied. The temperature rose to 150° and then gradually fell to below 60°. The mixture was then heated for 3 hr at 80°. The brown solution was cooled in ice, basified carefully with 3 *N* NaOH and extracted with $CH_2Cl_2$. After washing with 0.1 *N* HCl and water, the organic layer was separated, dried ($Na_2SO_4$), and filtered through 100 g of Florisil. Evaporation of the solvent gave an amber oil which was treated with ether and refrigerated. Filtration gave 6.4 g (17%) of pale yellow prisms, mp 195–199°. Recrystallization from ethanol gave white prisms, mp 195–198°.

*Anal.* Calcd for $C_{15}H_{10}FNO$: C, 75.30; H, 4.21. Found: C, 75.10; H, 4.29.

(13) A. K. Kiang, F. G. Mann, A. F. Prior, and A. Topham, *J. Chem. Soc.*, 1319 (1956).

(14) All melting points are corrected and were taken in capillary tubes on a Thomas–Hoover melting point apparatus. Infrared spectra were determined using a Beckman IR-9 spectrophotometer, nmr spectra with a Varian A-60 spectrometer, mass spectra with a CEC 21-100 spectrometer, and ultraviolet spectra with a Cary Model 14 spectrophotometer. The ultraviolet $\epsilon$ values refer to $\epsilon \times 10^{-3}$.

**B. From Indolylmagnesium Bromide and *o*-Fluorobenzoyl Chloride.**—To phenylmagnesium bromide, prepared from 24.3 g (1 g-atom) of magnesium and 176 g (1.1 mol) of bromobenzene in 300 ml of ether, was added dropwise with stirring, 130 g (1.1 mol) of indole in 300 ml of benzene. The resultant solution was heated under gentle reflux for 1 hr and cooled in ice, and 179 g (1.1 mol) of *o*-fluorobenzoyl chloride in 200 ml of benzene was added with vigorous stirring during 2 hr. The resultant mixture was heated under gentle reflux for 45 min, then cooled in ice, and hydrolyzed by the addition of 400 ml of 10% $NH_4Cl$ in water. The reddish solid[15] was filtered, washed with water and ether, and then hydrolyzed by heating on the steam bath for 20 min with a mixture of 600 ml of acetone–100 ml of methanol and 200 ml of 5% NaOH. The resultant mixture was poured into 1800 ml of water and, after cooling, was filtered and recrystallized from acetone–methanol to yield 54 g of **1** as off-white prisms, mp 195–197°.

The filtrate obtained after separating the red solid and its ether washings were combined and the organic layer was separated, washed, dried, and concentrated. The resultant red, viscous mixture was triturated with hot ethanol, cooled, and filtered to give white crystals of 1,3-di(*o*-fluorobenzoyl)indole, mp 132–134°.

*Anal.* Calcd for $C_{22}H_{13}F_2NO_2$: C, 73.13; H, 3.63; N, 3.85. Found: C, 73.25; H, 3.72; N, 3.90.

The solid was hydrolyzed by warming it on the steam bath for 20 min in a mixture of 300 ml of acetone and 150 ml of 10% NaOH. After pouring into water the mixture was filtered to give 56 g of **1**, mp 195–198°. The total yield of product was 110 g (46%).

**1-Methyl-3-(2-fluorobenzoyl)indole (2).**—A stirred solution of 9 g (0.038 mol) of **1** in 450 ml of acetone was treated with a solution of 41 g of KOH in 200 ml of water followed by the dropwise addition of 36 ml of dimethyl sulfate. After stirring for 30 min at room temperature the acetone was removed at reduced pressure, and the resultant precipitate was filtered, washed with water, and recrystallized from methanol to yield 6.1 g (63%) of white needles, mp 105–107°.

*Anal.* Calcd for $C_{16}H_{12}FNO$: C, 75.87; H, 4.78. Found: C, 76.05; H, 4.59.

**5-(3-Indolyl)-2,3-dihydro-1H-1,4-benzodiazepine (3).**—A solution of 100 g (0.436 mol) of **1**, 500 ml of pyridine, and 234 ml of ethylenediamine was heated under reflux for 20 hr. The solution was concentrated at reduced pressure, and the resultant oily residue was dissolved immediately in 1 l. of hot $CH_2Cl_2$. After overnight refrigeration, filtration gave 49 g of **3** as pale yellow needles, mp 212–216°. Recrystallization from ethanol–water raised the melting point to 223–225°.

*Anal.* Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.09; H, 5.46; N, 16.09.

The dichloromethane filtrate was concentrated to dryness and the residue hydrolyzed by heating under reflux for 5 hr with a mixture of 250 ml of ethanol and 250 ml of 2 *N* $H_2SO_4$. After cooling, the precipitate was filtered and washed to give 17 g of **1**. On the basis of recovered starting material, the yield of **3** was 54%.

**1-Methyl-3-[2-(benzylamino)benzoyl]indole (4).**—A solution of 20 g (0.08 mol) of **2** in 50 ml of pyridine and 36 ml of benzylamine was heated under reflux for 20 hr. The mixture was concentrated under reduced pressure to remove excess solvent, and the residue was treated with 100 ml of ethanol and 100 ml of 2 *N* sulfuric acid. The resultant mixture was refluxed for 8 hr and then concentrated to small volume. The residue was extracted with $CH_2Cl_2$, washed with water, dried over sodium sulfate, and concentrated to a yellow oil. This oil was dissolved in 75 ml of 2-propanol and refrigerated. Filtration gave 13.4 g of impure yellow solid. The solid was dissolved in benzene and placed on silica gel, and the silica gel was washed with *ca.* 2 l. of methylene chloride. Evaporation of the solvent gave 8.9 g (33%) of yellow solid, mp 133–135°. Recrystallization from 2-propanol yielded yellow prisms, mp 133–135°.

*Anal.* Calcd for $C_{23}H_{20}N_2O$: C, 81.29; H, 5.86; N, 8.11. Found: C, 81.15; H, 5.92; N, 8.23.

**1-Benzyl-3-(2-methylaminophenyl)-4(1H)-quinolone (5) and 5-Benzyl-11-methyl-11H-indolo[3,2-*c*]quinolinium Chloride (6).**—A solution of 10.2 g (0.03 mol) of **4** in a mixture of 175 ml of 6 *N* HCl and 200 ml of methanol was heated under reflux for 4 hr. The methanol was removed under reduced pressure, and the residue was cooled in ice and basified with 10% NaOH. The resultant precipitate was filtered. This precipitate was suspended in hot $CH_2Cl_2$ and filtered, and the undissolved solid was washed with additional $CH_2Cl_2$. The organic filtrate was dried over sodium sulfate and filtered through 120 g of neutral Woelm alumina, and the alumina was washed with 500 ml of $CH_2Cl_2$ and then 500 ml of $CHCl_3$. Evaporation of the solvent and addition of 50 ml of ether to the residue gave 4.4 g of **5** as a pale yellow solid, mp 205–211°. Recrystallization from methanol–dichloromethane gave white prisms: mp 213–215°; nmr (DMSO-$d_6$), $\delta$ 8.33 (s, 1, C=**CH**—N—$CH_2C_6H_5$), 5.03 (m, 1, $J$ = 4.5 Hz, **H**–N–$CH_3$), and 2.72 (d, 3, $J$ = 4.5 Hz, NH–**$CH_3$**); uv max (2-propanol), 213 m$\mu$ ($\epsilon$ 46.1), 241 (28.7), 296 (infl) (9.8), 326 (14.0), and 340 (infl) (12.5); (0.1 *N* HCl), 214 (32.9), 261 (32.5), 310 (infl) (8.7), 329 (13.4), and 339 (12.1); (0.1 *N* KOH), 242 (31.0), 296 (infl) (8.5), 327 (13.1), and 339 (33.9).

*Anal.* Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.03; H, 6.06; N, 8.02.

The solid (1.5 g) undissolved by the $CH_2Cl_2$ was recrystallized from methanol–ether to give white needles, mp 278–284°. This quaternary salt failed to give satisfactory microchemical data, and therefore it was converted into its chloride by suspending it in water with 5 g of freshly prepared silver chloride. After heating at 55° for 1 hr, the mixture was filtered and the filtrate was concentrated to give white crystals, mp 278–282°. Recrystallization from methanol gave colorless needles, mp 288–291°.

*Anal.* Calcd for $C_{23}H_{19}ClN_2$: C, 76.98; H, 5.34; N, 7.81. Found: C, 77.11; H, 5.35; N, 7.87.

Vacuum sublimation of **6** at 210–220° (0.1 mm) gave 11-methyl-11H-indolo[3,2-*c*]quinoline, as the sublimate, mp 142–144° (lit.[13] mp 146°); when mixed with an authentic sample, the melting point was 140.5–142°; the infrared spectra were identical.

*Anal.* Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.84; H, 5.25; N, 11.89.

**1-(2-Aminoethyl)-3-(2-aminophenyl)-4(1H)-quinolone (7). A. By Hydrolysis of 3.**—A solution of 5 g (0.019 mol) of **3** dissolved in a mixture of 25 ml of ethanol and 25 ml of 2 *N* sulfuric acid was heated under reflux for 32 hr and concentrated. The residual solid was dissolved in water, basified with 2 *N* NaOH and extracted with $CH_2Cl_2$. The organic layers were combined, washed with water, and dried over sodium sulfate. The solvent was concentrated to a small volume and ether was added until a solid began to separate. Refrigeration and filtration gave 3.5 g (70%) of yellow crystals, mp 163–165°. Recrystallization twice from ethanol–ether gave pale yellow needles: mp 162.5–163.5; ir (KBr), 3370, 3350, 3300 ($NH_2$), and 1610 $cm^{-1}$ (C=O); nmr (DMSO-$d_6$), $\delta$ 8.05 (s, 1, =**CH**—N—$CH_2$—), 4.82 (s, 2, **$H_2$**N—C$\leq$), and 2.13 (broad, 2, **$H_2$**N—$CH_2$—); uv max (2-propanol), 215, m$\mu$ ($\epsilon$ 36.5), 235 (sh) (24.0), 255 (sh) (19.8), 297 (10.3), 333 (11.0), and 343 (sh) (10.55); (0.1 *N* HCl), 216 (25.4), 258 (32.2), 300 (sh) (6.2), 327 (12.0), and 338 (11.5); (0.1 *N* KOH) 235 (26.3), 245 (sh) (25.0), 294 (sh) (7.8), 328 (11.1), and 340 (10.7).

*Anal.* Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 72.85; H, 6.24; N, 15.25.

**B. By Reduction of 20.**—A solution of 1.0 g (0.003 mol) of **20**, prepared as described below, in 25 ml of ethanol was hydrogenated at 25° and atmospheric pressure using 0.5 g of Raney nickel. The reduction was stopped after 204 ml (0.09 mol) of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent was concentrated to small volume, diluted with ether until slightly turbid, and refrigerated. Filtration gave 0.8 g (89%) of pale yellow prisms, mp 85–95° (possibly an etherate). Upon vacuum drying at 70° overnight, the melting point was raised to 159–160.5°. The mixture melting point with the product obtained by hydrolysis of **3** was 161–163°.

**5-(2-Aminoethyl)-5H-indolo[3,2-*c*]quinoline (8). A.**—A solution of 20 g (0.075 mol) of **3** dissolved in a mixture of 200 ml of 6 *N* HCl and 150 ml of ethanol was heated under reflux for 9 days and then concentrated to remove the alcohol. The residue was basified with concentrated $NH_4OH$, and the resultant oily suspension was refrigerated for several days. Filtration gave a yellow-brown solid which was recrystallized by dissolving it in methanol (a small amount of undissolved oil was discarded) and adding water until the mixture was slightly turbid (a small quantity of dark, amorphous solid which separated during the addition of water was discarded). After refrigeration, filtration yielded 11.3 g of yellow-green solid, mp (softens at 80°) 162–164°. The analytical sample was recrystallized from tetrahydrofuran–ether to give

(15) Tlc on silica gel G using ethyl acetate–hexane (1:1) showed this solid to be a mixture of compound **1** plus 1,3-di(*o*-fluorobenzoyl)indole.

yellow needles: melting point softens from *ca.* 150° until completely melted at 175°; nmr (DMSO-$d_6$), $\delta$ 9.20 (s, 1, =CH—N—$CH_2$); uv max (2-propanol), 220 m$\mu$ ($\epsilon$ 22.9), 237 (23.8), 248 (20.7), 280 (infl) (29.5), 291 (53.9), 303 (infl) (14.0), 318 (14.4), 340 (6.9), 363 (infl) (7.3), and 380 (7.6); (0.1 *N* HCl), 223 (22.5), 234 (28.7), 254 (infl) (21.4), 275 (32.7), 284 (33.4), 300 (13.0), and 350 (10.3); (0.1 *N* KOH) 219 (22.9), 241 (28.75), 280 (infl) (32.0), 288 (55.2), 312 (15.0) 330 (flat) (6.3), and 372 (9.5).

*Anal.* Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.03; H, 6.07; N, 16.04.

**B.**—A solution of 9.7 g of **7** in 100 ml of ethanol and 100 ml of 2 *N* $H_2SO_4$ was heated under reflux for 66 hr and then concentrated to remove the alcohol. The residue was basified and the precipitate filtered and air dried. Recrystallization from chloroform–ether gave yellow needles, mp 165–169°, identical in all respects with the product obtained by procedure A.

**11H-Indolo[3,2-*c*]quinoline (9) and 3-(2-Aminophenyl)-4(1H)-quinolone (10).**—A solution of 11.2 g of **7** in 100 ml of nitrobenzene was heated under reflux for 21.5 hr. The black solution was cooled to room temperature and 100 ml of ether added. After refrigeration the mixture was filtered to give 3.9 g of a dark brown solid. This solid was dissolved in methanol, filtered from an undissolved residue (discarded), and the filtrate diluted with ether. The precipitated brown solid was recrystallized several times from benzene–methanol to give 290 mg of **10** as pale yellow plates: mp 258–260°; ir (KBr), 3390, 3200 ($NH_2$, NH) and 1620 cm$^{-1}$ (C=O); nmr (DMSO-$d_6$), $\delta$ 4.83 (broad s, 2, $-NH_2$), 7.95 (s, 1, =CH—N—), and 4.83 (broad s, 1, HN—CH=); uv max (2-propanol), 235 m$\mu$ ($\epsilon$ 22.5), 251 (22.3), 280 (infl) (20.2), 300 (10.5), 323 (10.8), and 335 (9.75).

*Anal.* Calcd for $C_{15}H_{12}N_2O$: C, 76.24; H, 5.12; N, 11.86. Found: C, 76.31; H, 5.39; N, 11.77.

The nitrobenzene–ether filtrate was concentrated at reduced pressure and the residue was dissolved in dichloromethane. This solution was extracted with 2 *N* hydrochloric acid and the acid layer was basified and extracted with dichloromethane. Concentration to small volume gave *ca.* 100 mg of **9**: mp 339–341° (lit.[9] mp 342°); mixture melting point with an authentic specimen, 341–343°.

**5-(3-Indolyl)-2,3-dihydro-4-methyl-1H-1,4-benzodiazepinium Iodide (11).**—A stirred solution of 26 g (0.1 mol) of **3** in 300 ml of warm tetrahydrofuran was treated with 30 ml (excess) of methyl iodide and heated under reflux for 2.5 hr. After cooling to room temperature, the suspension was filtered to give an orange solid. Recrystallization from methanol gave 23.5 g (58%) of yellow plates, mp 255–263°. An additional recrystallization from methanol raised the melting point to 259–263°.

*Anal.* Calcd for $C_{18}H_{18}N_3I$: C, 53.61; H, 4.50; N, 10.42. Found: C, 53.61; H, 4.25; N, 10.05.

**3-[2-(2-Methylaminoethylamino)benzoyl]indole (12).**—To a suspension of 32 g (0.08 mol) of **11** in 400 ml of methanol was added with swirling 160 ml (0.16 mol) of 1 *N* NaOH. After approximately 30–40 min at room temperature, the resultant solution began to deposit a yellow solid. The suspension was allowed to stand for an additional hour at room temperature and then refrigerated. The precipitate was separated by filtration, washed with water, and dried to yield 20.6 g of bright yellow crystals, mp 144–146°. Upon standing the filtrate gave an additional 2 g of product. The total yield was 22.6 g (96.5%). The analytical sample was obtained by recrystallization from benzene to give yellow plates: mp 146–147°; ir ($CHCl_3$), 3470, 3340 ($NH_2$), and 1620 cm$^{-1}$ (C=O); uv max (2-propanol), 209 m$\mu$ ($\epsilon$ 41.9), 235 (26.1), 270 (infl) (11.6), 311 (10.2), and 377 (7.85); (0.1 *N* NaOH) 235 (infl) (2.0), 271 (15.15), and 343 (14.2).

*Anal.* Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 74.05; H, 6.56; N, 14.27.

**1-(2-Methylaminoethyl)-3-(2-aminophenyl)-4(1H)-quinolone (13) and 5-(2-methylaminoethyl)-5H-indolo[3,2-*c*]quinoline (14) Dihydrochloride.**—A solution of 10 g (0.034 mol) of **12** in 150 ml of 2 *N* $H_2SO_4$ and 100 ml of methanol was heated under reflux for 8.5 hr and then concentrated to remove the alcohol. The residue was basified with 10% sodium hydroxide and extracted with chloroform. The organic layer was separated, washed with water, dried over sodium sulfate, and evaporated. The residual yellow solid was suspended in 50 ml of ether, heated to boiling, and filtered. The separated solid was washed with an additional 200 ml of ether and then recrystallized from benzene to give 6 g (60%) of **13** as colorless plates: mp 175–176°, ir ($CHCl_3$), 3410, 3360 ($NH_2$), and 1620 cm$^{-1}$ (C=O); uv max (2-propanol), 214 m$\mu$ ($\epsilon$ 35.1), 234 (infl) (21.7), 250 (sh) (8.9), 294 (9.9), 330 (10.9), and 340 (sh) (10.0); (0.1 *N* HCl), 215 (25.7), 259 (32.25), 304 (sh) (7.0), 327 (12.5), and 339 (11.1).

*Anal.* Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.67; H, 6.30; N, 14.21.

Evaporation of the combined ether washes gave 0.7 g of a yellow oil. This oil was covered with an excess of methanolic hydrogen chloride and refrigerated. The solid was filtered to give 0.6 g of **14** as the hemihydrate of the dihydrochloride. Recrystallization from methanol gave white needles: mp (darkening *ca.* 280°) 292–297° dec; uv max ($H_2O$), 216 m$\mu$ (infl) ($\epsilon$ 20.4), 223 (infl) (23.4), 235 (30.3), 254 (infl) (22.0), 275 (34.6), 283 (35.7), 299 (infl) (14.4), and 350 (10.9); (0.1 *N* KOH), 218 (23.9), 241 (30.0), 278 (infl) (33.0), 288 (57.9), 300 (infl) (16.2), 317 (16.15), 334 (6.75), and 370 (9.9); (0.1 *N* HCl), 215 (infl) (20.5), 223 (infl) (24.0), 235 (30.75), 254 (infl) (22.7), 275 (35.4), 283 (36.5), 300 (15.0), and 350 (11.4); nmr ($D_2O$), $\delta$ 9.42 (s, 1, =CH—N—$CH_2$).

*Anal.* Calcd for $C_{18}H_{19}Cl_2N_3 \cdot 0.5H_2O$: C, 60.50; H, 5.59; N, 11.75. Found: C, 60.34; H, 5.47; N, 11.84.

**Ethyl 3-Hydroxy-2-(2-nitrophenyl)acrylate (16).**—A solution of 104.5 g (0.5 mol) of ethyl 2-nitrophenylacetate and 104.5 g (0.71 mol) of the diethyl acetal of N,N-dimethylformamide[11] was heated under reflux for 3 days and concentrated. The residual brown oil was dissolved in a mixture of 150 ml of ethanol and 150 ml of 12 *N* $H_2SO_4$ and let to stand at room temperature for 3 hr. The solution was then diluted with 500 ml of ether and 300 ml of water. The dark red organic layer was separated, washed with water, and then extracted with a saturated sodium carbonate solution until all of the red color was in the aqueous phase. The ether layer was concentrated to give 16 g of starting material. The alkaline extracts were combined, neutralized with acid, and extracted with ether. The organic layer was separated, washed, dried, and concentrated to give 70.1 g (70%, based upon unrecovered starting material) of yellow prisms, mp 95.5–98°. Recrystallization from benzene gave yellow prisms: mp 95.5–98°; nmr (DMSO-$d_6$), $\delta$ 7.88 (s, 1, =CH—O—H) and 9.67 (broad s, 1, $\geq$C—OH).

*Anal.* Calcd for $C_{11}H_{11}NO_5$: C, 55.69; H, 4.67; N, 5.91. Found: C, 55.76; H, 4.32; N, 5.68.

**Ethyl 3-Anilino-2-(2-nitrophenyl)acrylate (17).**—A mixture of 100 g (0.422 mol) of **16** and 39.5 g (0.422 mol) of aniline was heated on a steam bath until solution occurred, 100 ml of ethanol was added, and the solution was let to stand overnight at room temperature. The precipitate was filtered to give 106 g of **17** as red prisms, mp 130–135°. The analytical sample was obtained by recrystallization from ethanol to give orange rods, mp 135–138°.

*Anal.* Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.46; H, 5.02; N, 9.03.

Evaporation of the ethanol filtrate gave a yellow-orange solid which was washed with ether to give 22.5 g of the second isomer of **17**, mp 115–120°. Recrystallization from ethanol gave orange plates, mp 115–117°; total yield, 128.5 g (97%).

*Anal.* Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.60; H, 5.03; N, 9.09.

**3-(2-Nitrophenyl)-4(1H)-quinolone (18).**—A solution of 17.5 g (0.056 mol) of **17** in 200 ml of diphenyl ether was heated under reflux for 4 hr. The ethanol generated during the reaction was removed using a Dean–Stark trap. After standing overnight at room temperature, the product was separated by filtration. The precipitate was washed with ether and dried to give 3.6 g (24%) of yellow crystals, mp 286–288°. Recrystallization from ethanol gave yellow microneedles, mp 287–288°.

*Anal.* Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.45; H, 3.38; N, 10.32.

**3-(2-Aminophenyl)-4(1H)-quinolone (10) by Reduction of 18.**—A solution of 0.8 g of **18** in 150 ml of methanol was treated with 1.5 g of Raney nickel and reduced at atmospheric pressure until the theoretical uptake of hydrogen had been absorbed. The mixture was filtered over Celite and the filtrate concentrated to give 0.6 g of white plates, mp 267–269°. This product was identical in all respects with the product obtained by pyrolysis of **3** in nitrobenzene.

**1-[2-(Benzyloxycarbonylamino)ethyl]-3-(2-nitrophenyl)-4(1H)-quinolone (19).**—A solution of 8.6 g (0.032 mol) of **18** in 50 ml of dry DMF was treated under nitrogen with 1.62 g (0.032 mol) of a 50% dispersion of sodium hydride in mineral oil. The resultant solution was stirred at room temperature for 1 hr and then

treated with a solution of 11.6 g (0.043 mol) of carbobenzoxy-2-bromoethylamine[16] in 10 ml of DMF. The reaction mixture was then heated at 80° for 66 hr, poured into a stirred mixture of 300 g of cracked ice and 300 ml of water, and filtered. The precipitate was washed with water and dried to yield 4.9 g (34%) of yellow solid, mp 172–177°. Recrystallization from benzene–methanol gave bright yellow rods, mp 174.5–175.5°.

*Anal.* Calcd for $C_{25}H_{21}N_3O_5$: C, 67.71; H, 4.77; N, 9.48. Found: C, 67.78; H, 4.85; N, 9.32.

**1-(2-Aminoethyl)-3-(2-nitrophenyl)-4(1H)-quinolone (20).**—A saturated solution (50 ml) of hydrogen bromide in glacial acetic acid was treated with 4.9 g (0.011 mol) of **19**. The reaction mixture was stirred overnight at room temperature and then diluted with ether. The product, as the hydrobromide salt, was removed by filtration and dissolved in 1500 ml of water, basified with concentrated $NH_4OH$, and extracted with $CH_2Cl_2$. The organic layer was washed with water, dried over sodium sulfate, filtered, and evaporated. The crystalline residue was filtered and the precipiate was washed with dichloromethane to yield 2.7 g (79%) of product, mp 202–204°. Recrystallization from ethanol gave yellow prisms, mp 203–204°.

*Anal.* Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 66.32; H, 5.09; N, 13.44.

**1-Benzyl-3-(2-nitrophenyl)-4(1H)-quinolone (21).**—To a stirred solution of 11.5 g (0.044 mol) of **18** in 200 ml of DMF was added, under nitrogen, 2.2 g (0.046 mol) of 50% sodium hydride. After stirring at room temperature for 1 hr, 7.4 g (0.044 mol) of benzyl bromide was added and the mixture was stirred for an additional 2 hr and then poured into ice–water. The precipitate was filtered, washed with water, and recrystallized from methanol–dichloromethane to yield 13.3 g (86.5%) of yellow crystals, mp 186–187.5°.

*Anal.* Calcd for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.53; N, 7.86. Found: C, 74.35; H, 4.72; N, 8.12.

**3-(2-Aminophenyl)-1-benzyl-4(1H)-quinolone (22).**—A solution of 8.3 g (0.023 mol) of **21** in 600 ml of methanol was hydrogenated at 25° and atmospheric pressure using 1 g of Raney nickel. The reduction was stopped after 1500 ml (theoretical 1570 ml) of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate concentrated. The residue was recrystallized from methanol to give 6.6 g (87%) of yellow prisms: mp 189–191°; ir ($CHCl_3$), 3410 and 3300 $cm^{-1}$ ($NH_2$).

*Anal.* Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.88; H, 5.76; N, 8.30.

**1-Benzyl-3-[2-(*p*-toluenesulfonamido)phenyl]-4(1H)-quinolone (23).**—To a solution of 5 g (0.015 mol) of **22** in 50 ml of pyridine was added 3 g (0.015 mol) of *p*-toluenesulfonyl chloride. After standing overnight at room temperature, the resultant mixture was poured into water, let stand for 2 hr, and filtered. The solid was washed thoroughly with water recrystallized twice from methanol to yield white prisms, mp 188–190°.

*Anal.* Calcd for $C_{29}H_{24}N_2O_3S$: C, 72.48; H, 5.03; N, 5.83. Found: C, 72.17; H, 4.91; N, 5.83.

**1-Benzyl-3[2-(N-methyl-*p*-toluenesulfonamido)phenyl]-4(1H)-quinolone (24).**—To a solution of 3.5 g (0.008 mol) of **23** in 20 ml of DMF was added, under nitrogen, 0.35 g (0.008 mol) of 50% sodium hydride. After stirring at room temperature for 1 hr, 1.03 g (0.008 mol) of methyl iodide was added, and the mixture was stirred for 2 hr at room temperature and then poured into ice–water. The precipitate was recrystallized from 2-propanol to yield 3.5 g (87%) of off-white prisms, mp 171–174°.

*Anal.* Calcd for $C_{30}H_{26}N_2O_3S$: C, 72.85; H, 5.30; N, 5.66. Found: C, 72.70; H, 5.39; N, 5.62.

**1-Benzyl-3-(2-methylaminophenyl)-4(1H)-quinolone (5) by Hydrolysis of 24.**—A mixture of 3 g (0.006 mol) of **24** in 15 ml of concentrated $H_2SO_4$ was heated on the steam bath for 15 min and poured into ice. The resultant solution was neutralized with concentrated $NH_4OH$, and the precipitate was filtered and washed thoroughly with water. Recrystallization from methanol gave colorless prisms, mp 212–214°; the mixture melting point with the product obtained by hydrolysis of **4** was 212–215°.

**5-(2-Diethylaminoethyl)-5H-indolo[3,2-*c*]quinoline (25) Dimethiodide.**—A solution of 40 g (0.17 mol) of **1** in a mixture of 50 ml of N,N-diethylethylenediamine and 100 ml of pyridine was refluxed for 17.5 hr and concentrated under reduced pressure. The viscous, oily residue was dissolved in $CH_2Cl_2$, washed thoroughly with water, dried, and concentrated. This residue was covered with 100 ml of ethanol and 100 ml of 2 *N* $H_2SO_4$ and refluxed, with stirring, for 5 hr. After cooling to room temperature, the precipitate was filtered, washed with 2 *N* $H_2SO_4$, water, and then recrystallized from methanol to yield 17.5 g of unreacted **1**. The alcohol–sulfuric acid filtrate was concentrated to remove the alcohol and the residue basified with 10% NaOH and extracted with dichloromethane. The organic layer was separated, washed (water, brine), and dried ($Na_2SO_4$). Evaporation of the solvent yielded 12.3 g of viscous oil. The oil was dissolved in benzene and chromatographed on 500 g of grade I neutral Woelm alumina. Elution of the column with benzene–dichloromethane (1:1) gave 5 g of **25**; uv max (2-propanol), 217 mμ (ε 15.0), 236 (14.8), 248 (sh) (12.9), 280 (infl) (19.0), 291 (30.9), 305 (infl) (8.6), 316 (8.7), 339 (4.8), and 365–380 (4.8); (0.1 *N* HCl), 215 (infl) (15.5), 222 (infl) (17.0), 235 (19.8), 255 (15.1), 276 (21.8), 284 (22.2), 300 (9.6) and 351 (7.25); (0.1 *N* KOH), 218 (13.9), 242 (18.0), 278 (infl) (19.0), 288 (33.6), 312 (9.9), 335 (infl) (4.4), and 372 (6.2).

Continued elution with ethyl acetate gave a mixture of **25** plus several other compounds, as observed by tlc. Evaporation of the ethyl acetate and addition of ether precipitated 200 mg of indolo[3,2-*c*]quinoline (**9**), mp 337–339°, undepressed when mixed with an authentic specimen. The remaining products could not be separated and identified.

Compound **25** was converted into its dimethiodide by treating 0.5 g of this compound, as an oil, with 0.4 g of methyl iodide in 10 ml of nitrobenzene. After warming on the steam bath for 20 min, the mixture was cooled and filtered. The precipitate was washed with ether and recrystallized from water to give white needles, mp 250–252° dec (lit.[9] mp 263–264°); mixture melting point with an authentic sample (mp 245–246° dec) was 247–248° dec; infrared spectra were identical.

**5-(1-Methyl-3-indolyl)-2,3-dihydro-1H-1,4-benzodiazepine (26).**—A solution of 5.5 g (0.02 mol) of **2** in 20 ml of ethylenediamine and 40 ml of pyridine was refluxed for 18 hr and evaporated. The residue was partitioned between $CH_2Cl_2$ and water. The organic layer was separated, washed, and extracted with three 100-ml portions of 1 *N* HCl. The acid extract was basified with $NH_4OH$ and extracted with dichloromethane. After being washed and dried the dichloromethane was concentrated to a small volume, petroleum ether (bp 30–60°) was added until faintly turbid and the mixture was refrigerated. Filtration gave 2.7 g (46%) of bright yellow solid, mp 142–146°. An additional recrystallization from dichloromethane–petroleum ether gave small yellow plates, mp 144–148° (sinters prior to melting).

*Anal.* Calcd for $C_{18}H_{17}N_3$: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.48; H, 6.34; N, 15.23.

**2,3-Dihydro-9-methyl-9H-imidazo[1,2-*a*]indolo[3,2-*c*]quinoline (27).**—A solution of 10.3 g of **26** in 110 ml of ethanol and 110 ml of 6 *N* HCl was refluxed for 20.5 hr. After standing at room temperature overnight, the suspension was filtered to give 8 g of solid. Concentration of the filtrate to an oily solid and addition of a few milliliters of methanol gave an additional 1.6 g of solid. The two solids were combined, basified with a slight excess 1 *N* NaOH, and extracted with chloroform. The organic layer was separated, washed with a small amount of water, dried, and concentrated. The residual oil upon trituration with hot benzene gave a yellow solid. Recrystallization from 2-propanol–dichloromethane gave yellow needles: mp 257–260° dec; nmr (DMSO-$d_6$), δ 4.09 (s, 3, $CH_3$—N) and 3.96 (s, 4, =N—$CH_2$—$CH_2$—N).

*Anal.* Calcd for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N, 15.38. Found: C, 79.06; H, 5.71; N, 15.36.

**Registry No.**—**1,** 16273-87-3; **2,** 16273-88-4; **3,** 16274-02-5; **4,** 16273-89-5; **5,** 16273-90-8; **6,** 16273-91-9; **7,** 16273-92-0; **8,** 16273-93-1; **10,** 16273-94-2; **11,** 16273-95-3; **12,** 16273-96-4; **13,** 16273-97-5; **14** dihydrochloride, 16273-98-6; **16,** 16273-99-7; **17** (*cis*), 16274-00-3; **17** (*trans*), 16274-01-4; **18,** 16273-20-4; **19,** 16273-22-6; **20,** 16273-24-8; **21,** 16273-26-0; **22,** 16273-28-2; **23,** 16273-30-6; **24,** 16273-31-7; **25,** 16273-32-8; **26,** 16273-33-9; **27,** 16273-34-0; 1,3-di-(*o*-fluorobenzoyl)indole, 16273-36-2.

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# The Condensation of *o*-Benzoylbenzaldehyde with Aliphatic Diamines

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The reaction of *o*-benzoylbenzaldehyde (II) with aliphatic diamines gave condensation products of type V which could readily be oxidized *via* peroxides of type VI to the carbinolamine derivatives of type IXa. The equilibrium between the tautomeric imidazoline derivatives IXa and IXb was investigated.

The reaction of aromatic *o*-dialdehydes with aromatic *o*-diamines gives derivatives containing the imidazo[2,1-*a*]isoindole[1] ring system rather than eight-membered heterocyclic compounds claimed in some cases.[2] This reaction has recently been reinvestigated and Thiele's original assignment was confirmed.[3] A similar problem had arisen concerning the structure of the products obtained by condensation of *o*-benzoylbenzoic acid with ethylenediamine.[4] This led us to study the condensation of *o*-benzoylbenzaldehyde with aliphatic diamines.

The *o*-benzoylbenzaldehyde, compound II, was obtained in over 50% yield by the oxidation of the benzhydrol derivative I (Scheme I). On reaction with ethylenediamine in aqueous ethanolic solution the known phthalimidine derivative III[4b] was formed. This result is analogous to the formation of N-phenylphthalimidine on reaction of *o*-phthalaldehyde with aniline.[5]

When the condensation of *o*-benzoylbenzaldehyde with ethylenediamine was performed under anhydrous conditions, a product was obtained[6] to which we assigned structure V in analogy to the results obtained with phthalaldehyde and *o*-phenylenediamine.[1] Proof for this structure was supplied by preparing the same compound by cyclization of the phthalimidine derivative III using titanium tetrachloride as condensing agent. Compound III was not cyclized to V in boiling ethylenediamine and, therefore, is not an intermediate in the reaction II → V.

The free base V was rapidly oxidized by exposing it in various solvents to air or, more conveniently, by using hydrogen peroxide as the oxidant. The primary reaction product was the peroxide VI which could be isolated by chromatographic separation. The crude oxidation product always contained compound IX, which is most likely formed by a reduction of the intermediate peroxide VI. This peroxide liberated iodine from an acidified potassium iodide solution and was readily reduced to compound IX which on mild hydrolysis yielded the known 3-hydroxyphthalimidine derivative XIII.[4b] Confronted with the problem of deciding between structure a and b for IX, we found that infrared absorption at 1660 $cm^{-1}$ could not be accepted as proof for the presence of a carbonyl function since compounds V and VI also showed strong absorption at 1660 $cm^{-1}$ obviously due to C=N stretching. Near-infrared spectra[7] were measured in chloroform and the overtones of OH and NH absorption at 1.4 and 1.5 $\mu$, respectively, were found to be of equal intensity, indicating the presence of a 1:1 mixture of the forms IXa and b. As expected, this equilibrium proved to be pH dependent as shown by the ultraviolet spectra. On acidification a maximum at 251 m$\mu$ ($\epsilon$ 13,600) appeared which was attributed to the benzophenone chromophor and allowed the determination of a p$K$ 8.6.[8] This constant describes the equilibrium between the carbinolamine base IXa and the protonated keto form IXb. To remove all remaining doubt about the structure of IX, its hydrobromide was subjected to single crystal X-ray structure analysis[9] which showed that compound IX in its protonated form has the keto structure b. The formation of the ether XII observed on treatment of IX with methanol is a reaction typical for carbinolamines and proves the presence of the tautomer IXa in the equilibrium.

We propose that the equilibrium of IXa with IXb is determined by the competition between the intermolecular association of the amidine functions[10] and the intramolecular interaction of amine and carbonyl groups.

Ring homologs of IX were prepared by condensation of *o*-benzoylbenzaldehyde with the appropriate diamines and subsequent oxidation. As indicated by ultraviolet and near-infrared spectra, the increased size of the heterocyclic ring changes the character of the amidine functions sufficiently to force the expected equilibrium to the side of the carbinolamine structures (VII and VIII).

Another route for the preparation of compound IX was found by treating the condensation product of phthaldehydic acid and ethylenediamine (X) with phenyllithium. This reaction which presumably proceeds *via* the hypothetical intermediate d gave only a poor yield of IX. We, therefore, oxidized X with

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