Reaction of 2-Amino-7-chloro-5-phenyl-3*H*-[1,4]benzodiazepine with 1,3-Dicarbonyl Compounds[1]

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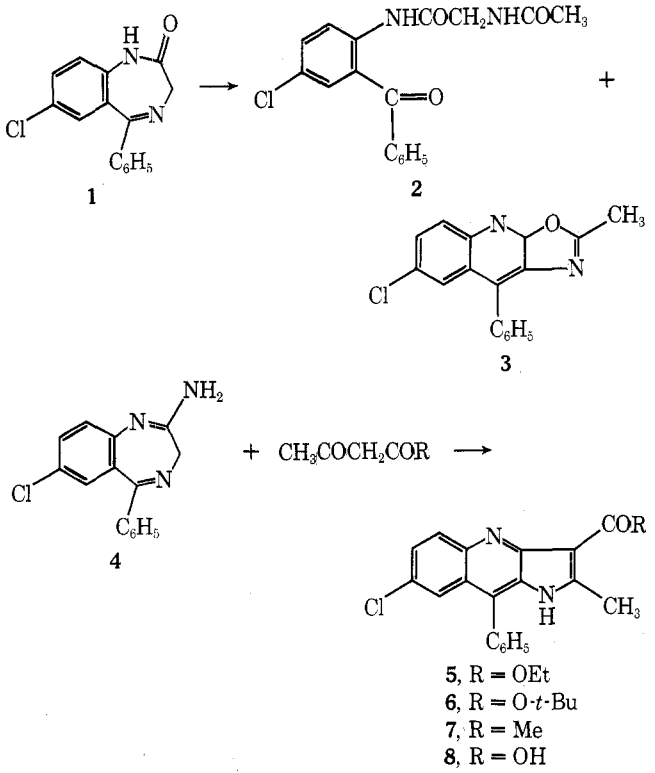
An interesting rearrangement was observed in the reaction of 2-amino-7-chloro-5-phenyl-3*H*-[1,4]benzodiazepines with 1,3-carbonyl compounds. On the basis of spectral data and chemical properties, the structures of the reaction products were assigned as possessing a rearranged ring system of 1*H*-pyrrolo[3,2-*b*]quinoline. The structure of one of these, namely the 1-[3-(dimethylamino)propyl] derivative of compound **5**, was confirmed by x-ray analysis.

A number of diverse rearrangements have been observed in the 1,4-benzodiazepine class of compounds.[2] One of these involved the transformation of compound **1** to anilide **2** and quinoline **3** when **1** was heated with acetic anhydride in the presence of either sulfuric acid or sodium acetate.[3]

We have now observed another example of the quinoline-type rearrangement. Thus, the reaction of 2-amino-7-chloro-5-phenyl-3*H*-[1,4]benzodiazepine (**4**) with ethyl acetoacetate, *tert*-butyl acetoacetate, and acetylacetone produced the 1*H*-pyrrolo[3,2-*b*]quinoline derivatives **5**, **6**, and **7** respectively.



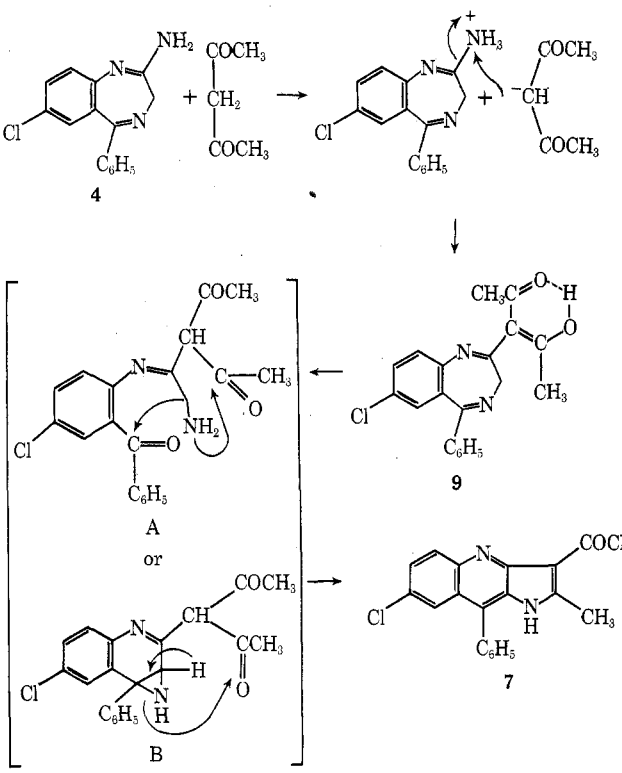
1 **2** **3** **4**

5, R = OEt
6, R = O-*t*-Bu
7, R = Me
8, R = OH

The proposed mechanism of this transformation in the case of the reaction of **4** with acetylacetone is shown in Scheme I. Initial displacement of the NH_2 group by an acetylacetone anion gave rise to compound **9**, which was isolated (as the enol) along with **7**. Compound **9** is visualized as rearranging to **7** either via the open-chain amino ketone A or via the aziridine B.

The structures of the rearrangement products **5**, **6**, and **7** are supported by spectroscopic data (see Experimental Section). For example, compound **6** showed a broad NH absorption at 2900 cm^{-1} and C=O at 1685 cm^{-1} in the infrared; extended conjugation in uv; C–CH_3 at δ 2.83, *tert*-butyl at δ 1.81, and no CH_2 or CH in the NMR; the mass spectrum gave a peak at *m/e* 41 (CH_3CN) indicative of N–C–CH_3 moiety. The ultraviolet spectra of **5**, **6**, and **7** were similar which indicated

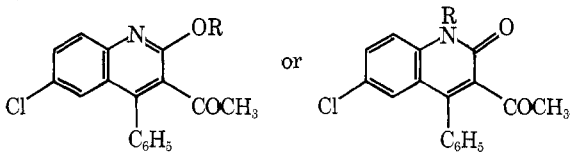
Scheme I



that these compounds possess the same chromophore and belong to the same structural class.

Treatment of **6** with trifluoroacetic acid gave the corresponding acid **8**.

From the reaction of **4** with *tert*-butyl acetoacetate a by-product was isolated and identified as **10** (**a** or **b**) by independent synthesis from 2-amino-5-chlorobenzophenone with either ethyl acetoacetate or *tert*-butyl acetoacetate. Compound **10** was alkylated with 2-dimethylaminoethyl chloride to give a compound which possesses either structure **11a** or **11b**.

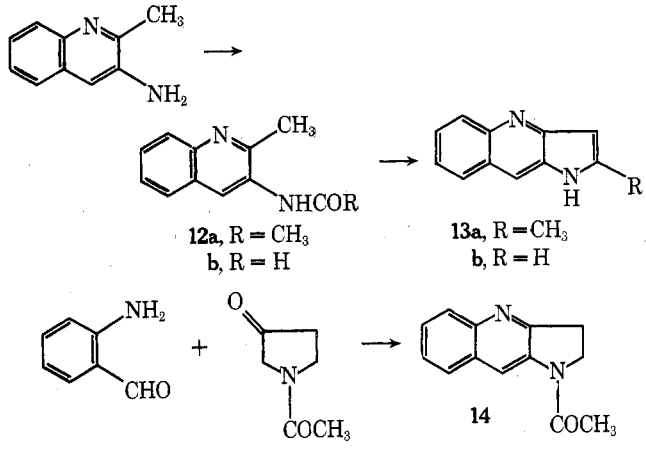


a **b**

10, R = H
11, R = $CH_2CH_2N(CH_3)_2$

The compounds described above appear to be the first examples of the 9-phenyl substituted-1*H*-pyrrolo[3,2-*b*]quinoline ring system. The corresponding dephenyl ring system (**13a,b**) was prepared earlier from 3-amino-2-methylquinoline by the Madelung reaction either via the 3-acetylamino (**12a**)[4]

or the 3-formylamino (**12b**)[5] derivatives. The analogous 2,3-dihydro ring system (**14**) had been prepared from *N*-acetyl-3-pyrrolidone and *o*-aminobenzaldehyde by the base-catalyzed Friedländer condensation.[6]



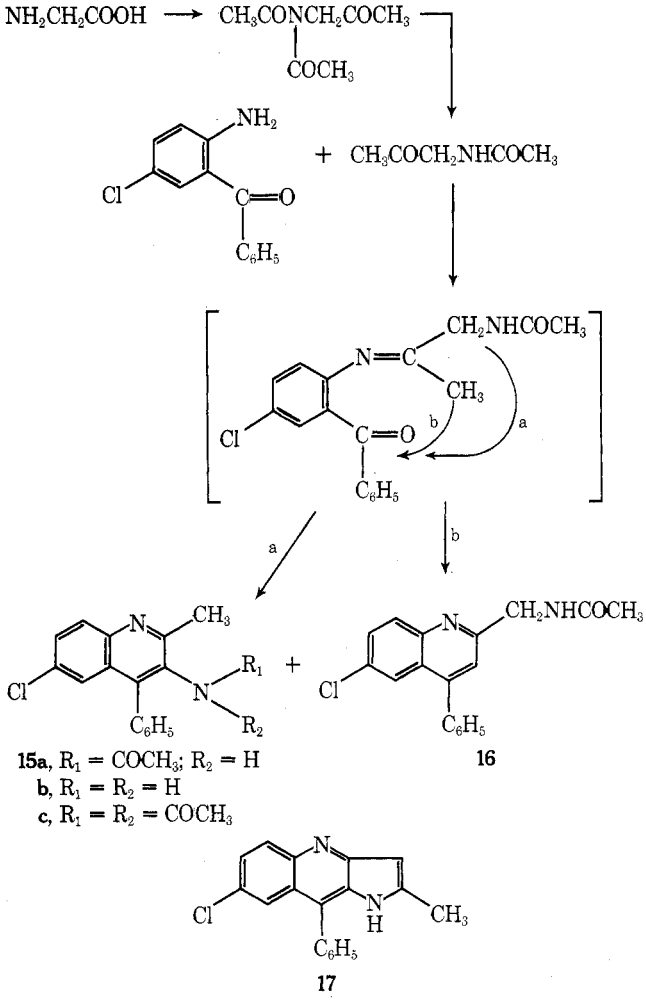
12a, R = CH_3
b, R = H

13a, R = CH_3
b, R = H

14

Our attempts to synthesize 7-chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinoline (**17**) for eventual comparison with the rearrangement products were terminated when it was found that the 1-[3-(dimethylamino)propyl] derivative of compound **5**, which formed triclinic crystals, was amenable to x-ray determination. Compounds **5** and **7** formed tetragonal crystals. Computer programs for determining their crystal structure were not readily available in our laboratory.

The attempts to synthesize **17** involved *N*-acetonylacetamide as a synthon for the construction of the suitably substituted quinoline ring system for a subsequent Madelung reaction. Thus, condensation of 2-amino-5-chlorobenzophenone with *N*-acetonylacetamide,[7] prepared from glycine in two steps, afforded a mixture of **15a** and **16**, easily separable by chromatography.



15a, R_1 = $COCH_3$; R_2 = H
b, R_1 = R_2 = H
c, R_1 = R_2 = $COCH_3$

16

17

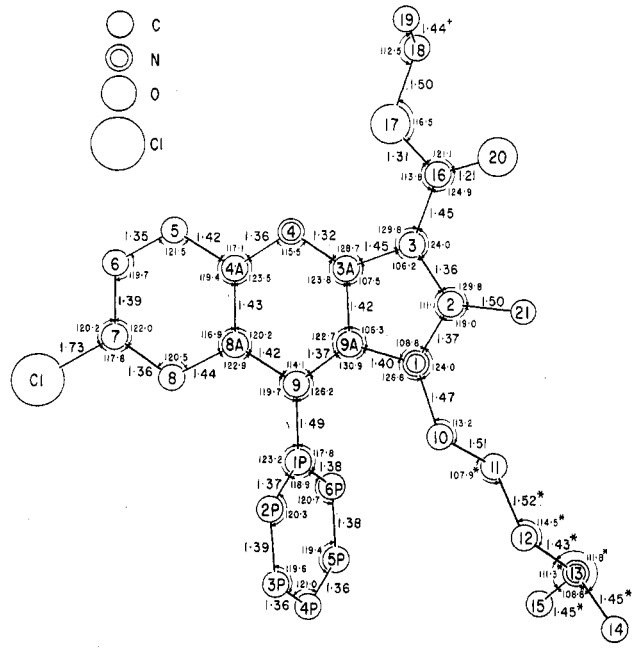


Figure 1. Mean bond distances (Å) and angles (degrees) for the two molecules. Standard deviations for distances are about 0.01 Å, for angles, about 0.5°. * Value obtained for unprimed molecule; + Corrected for thermal motion using "riding motion" mode.[13a]

Attempted reaction of **15** with sodamide in refluxing *N*,*N*-diethylaniline gave the deacetylated product, 3-amino-6-chloro-2-methyl-4-phenylquinoline (**15b**). The treatment of the *N*,*N*-diacetyl derivative **15c** with sodium ethoxide at 285 °C,[8] or treatment of **15a** with phosphorus oxychloride, followed by first dimethylacetamide and then potassium hydroxide,[9] also failed to yield **17**. A trace of the desired compound (**17**, M^+ *m/e* 292) along with its monochloro derivative (M^+ *m/e* 326) was found in the mass spectrum of the mixture obtained from the reaction of **15a** with phosphorus pentachloride in chloroform followed by treatment with triethylamine. A trace of the molecular ion M^+ *m/e* 292 was observed also from the products of the treatment of **15a** with potassium *tert*-butoxide at 255–270 °C.

In the course of these attempts the 1-*N*-oxide of **15a** was prepared but was not subjected to further experimentation.

Discussion of X-Ray Results. The structure of the 1-[3-(dimethylamino)propyl] derivative of **5** was determined by single-crystal x-ray analysis using direct methods. Final atomic coordinates are given in Table I. There are two symmetry-independent molecules which are very similar in conformation. The only difference worthy of note between the two is that the NMe_2 group in the molecule with primed numbers is probably disordered (see Experimental Section), as evidenced by exceptionally high anisotropic temperature factors.[10] Figure 1, which is drawn from x-ray coordinates, shows mean distances and angles. Hydrogens are not shown. The fused ring portion of the molecule is flat; the largest deviations from the least-squares planes calculated for the fused rings are 0.06 and 0.04 Å for C9 and C9′. The plane of the phenyl ring is approximately perpendicular (85 and 88°) to the plane of the fused rings. The carboxyl group is twisted about 10° out of the plane of the fused rings. The pattern of long and short bond lengths in the quinoline portion of the molecule is consistent with values reported in the literature for quinoline and acridine ring systems,[11,12] and can be explained by resonance structures.

Table I. Final Atomic Coordinates (× 10^4) for the 1-[3-(Dimethylamino)propyl] Derivative of 5. Standard Deviations are in Parentheses

	X	Y	Z
CL	7997 (2)	6174 (2)	12216 (1)
N(1)	6329 (5)	4425 (4)	8507 (2)
C(2)	5658 (6)	3462 (5)	8281 (3)
C(3)	5356 (6)	2772 (5)	8800 (3)
C(3A)	5870 (5)	3370 (5)	9413 (3)
N(4)	5800 (4)	3066 (4)	10046 (2)
C(4A)	6361 (6)	3804 (5)	10532 (3)
C(5)	6264 (6)	3522 (5)	11210 (3)
C(6)	6769 (6)	4213 (6)	11716 (3)
C(7)	7409 (6)	5235 (6)	11570 (3)
C(8)	7545 (5)	5557 (5)	10922 (3)
C(8A)	7004 (5)	4855 (5)	10362 (3)
C(9)	7114 (5)	5146 (5)	9675 (3)
C(9A)	6472 (5)	4413 (5)	9214 (3)
C(10)	6648 (6)	5411 (5)	8074 (3)
C(11)	7846 (6)	5211 (5)	7711 (3)
C(12)	7946 (6)	6185 (6)	7204 (3)
N(13)	9038 (6)	6121 (5)	6824 (3)
C(14)	8932 (8)	6880 (7)	6241 (4)
C(15)	10178 (8)	6434 (8)	7238 (4)
C(16)	4709 (6)	1666 (6)	8701 (3)
O(17)	4438 (5)	1184 (4)	9274 (2)
C(18)	3918 (9)	-43 (7)	9213 (3)
C(19)	2772 (12)	-121 (10)	9203 (8)
O(20)	4502 (5)	1137 (4)	8183 (2)
C(21)	5327 (6)	3307 (5)	7531 (3)
C(1P)	7856 (6)	6192 (5)	9510 (2)
C(2P)	7380 (6)	7299 (6)	9490 (3)
C(3P)	8122 (8)	8233 (6)	9306 (4)
C(4P)	9344 (8)	8042 (7)	9169 (4)
C(5P)	9862 (7)	6946 (8)	9198 (4)
C(6P)	9107 (6)	6018 (5)	9368 (3)
CL(')	1896 (2)	-977 (2)	6960 (1)
N(1')	3696 (5)	552 (4)	3408 (2)
C(2')	4377 (6)	1520 (5)	3235 (3)
C(3')	4677 (6)	2209 (5)	3787 (3)
C(3A')	4157 (5)	1650 (5)	4353 (3)
N(4')	4209 (4)	2007 (4)	5000 (2)
C(4A')	3631 (5)	1276 (5)	5413 (3)
C(5')	3705 (6)	1599 (5)	6119 (3)
C(6')	3187 (6)	919 (6)	6583 (3)
C(7')	2567 (6)	-106 (5)	6373 (3)
C(8')	2460 (6)	-471 (5)	5716 (3)
C(8A')	2991 (5)	222 (5)	5202 (3)
C(9')	2915 (5)	-126 (5)	4507 (3)
C(9A')	3544 (5)	610 (5)	4108 (3)
C(10')	3287 (7)	-384 (5)	2936 (3)
C(11')	2050 (9)	-128 (6)	2548 (4)
C(12')	1828 (9)	-1305 (8)	1961 (5)
N(13')	1103 (12)	-1104 (8)	1453 (5)
C(14')	869 (11)	-2120 (13)	1117 (7)
C(15')	269 (24)	-1075 (14)	1959 (11)
C(16')	5354 (6)	3332 (6)	3775 (3)
O(17')	5704 (4)	3768 (4)	4368 (2)
C(18')	6257 (8)	4974 (7)	4399 (4)
C(19')	7542 (9)	4926 (8)	4270 (4)
O(20')	5522 (5)	3840 (4)	3251 (2)
C(21')	4738 (7)	1623 (5)	2522 (3)
C(1P')	2181 (6)	-1196 (5)	4280 (2)
C(2P')	2728 (6)	-2291 (5)	4258 (3)
C(3P')	2016 (7)	-3259 (5)	4032 (3)
C(4P')	758 (8)	-3136 (7)	3867 (3)
C(5P')	201 (7)	-2075 (8)	3922 (4)
C(6P')	905 (7)	-1102 (6)	4126 (3)

Experimental Section

Melting points were taken in a capillary tube and are uncorrected. Uv spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. Ir spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. NMR spectra were recorded on a Varian Model A-60A; chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were recorded using a CH-4 Atlas mass spectrometer. The silica gel used for chromatography was obtained from E. Merck A. G., Darmstadt, Germany.

Ethyl 7-Chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinoline-3-carboxylate (5). A mixture of 2-amino-7-chloro-5-phenyl-3*H*-[1,4]benzodiazepine (**4**,[13b] 30 g, 0.112 mol) and 300 ml of ethyl acetoacetate was heated at 145–160 °C (oil bath temperature) for 3 h. It was then evaporated in vacuo at 95 °C. The residue was triturated with ethyl acetate, and the resulting solid was filtered and washed with ethyl acetate followed by ether, 9.8 g of pale yellow needles, mp 300–302 °C. The analytical sample was prepared from ethyl acetate: mp 300 °C dec; uv sh 238 nm (ε 40 800), λ_{max} 249 (53 500), 334 (12 500), 354 (9500), sh 368 (8350); ir NH ~2900 (broad); C=O 1685 (s); C=N/C=C 1630, 1595, 1550, 1500; C–O/C–N 1265, 1170, 1155, 1140, 1085, 1040; aromatic 830, 780, 740, 700 cm^{-1}; NMR (Me_2SO-d_6) δ 10.71 (broad, 1, NH), 8.6 (d, 1, aromatic H, J = 9.5 Hz), 7.84–7.42 (m, 7, aromatic H), 4.4 (q, 2, OCH_2, J = 7 Hz), 2.8 (s, 3, NC–CH_3), 1.4 (t, 3, OC–CH_3, J = 7 Hz); mass spectrum m/e 364 (M^+).

Anal. Calcd for $C_{21}H_{17}ClN_2O_2$: C, 69.13; H, 4.70; Cl, 9.72; N, 7.68. Found: C, 68.79; H, 4.74; Cl, 9.79; N, 7.44.

***tert*-Butyl 7-Chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinoline-3-carboxylate (6).** A mixture of **4** (20 g, 0.0743 mol) and 200 ml of *tert*-butyl acetoacetate was heated for 2 h at 151 °C (oil bath temperature), and evaporated in vacuo (ca. 0.1 mm). The residue was triturated with ethyl acetate to give 3.35 g: mp 289 °C, raised to 292 °C dec on recrystallization from chloroform; uv λ_{max} 205 nm (ε 34 650), sh 238 (38 750), 252 (52 400), sh 320 (7400), 334 (12 400), 354 (9250), sh 367 (8150); ir NH ~2900 (broad); C=O 1685 (s); C–O/C=N 1635 (w), 1600 (w), 1550 (m), 1505, 1480; C–N/C–O 1270, 1150, 1140, 1090, 1020; aromatic 830, 795, 710, 700 cm^{-1}; NMR (pyridine-d_5) δ 2.83 (s, 3, NC–CH_3), 1.8 (s, 9, *tert*-butyl); mass spectrum m/e 392 (M^+).

Anal. Calcd for $C_{23}H_{21}ClN_2O_2$: Cl, 9.02; N, 7.13. Found: Cl, 8.90; N, 7.26.

The filtrate from the original trituration (from a run one-tenth the scale of the above) was evaporated and the residue chromatographed on 300 g of silica gel using 5% MeOH–$CHCl_3$. Fractions 1–4 (400 ml total) gave a trace (discarded). Fractions 5–7 (25 ml each) afforded 41 mg of **6** after crystallization from ether. Fractions 8–10 (25 ml each) were crystallized from CH_2Cl_2–ether to give 64 mg of **10**, mp 274–275 °C. It was identical with the authentic sample prepared below by condensation of 5-chloro-2-aminobenzophenone and ethyl (or *tert*-butyl) acetoacetate as shown by comparison of TLC, ir, uv, NMR, and mass spectrum.

7-Chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinol-3-yl Methyl Ketone (7) and 3-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-4-hydroxy-3-penten-2-one (9). A mixture of **4** (2 g, 7.4 mmol) and 10 ml of acetylacetone was refluxed for 4 h and evaporated. The residue was chromatographed on 250 g of silica gel in 5% MeOH–$CHCl_3$. Fractions 1–2 (250 ml each) gave no material. Fractions 3–6 (25 ml each from now on) gave a trace (discarded). Fractions 7–8 gave 0.441 g of **9** which was crystallized twice from ether: 0.124 g, mp 175–176 °C; uv λ_{max} 218 nm (ε 28 200), sh 258 (14 100), sh 276 (10 200), 343 (25 500); ir C=O 1675, 1620, 1605, 1585, 1540, 1480; C–N/C–O 1355, 1325, 1320, 1220, 945; aromatic 835, 785, 740, 700 cm^{-1}; NMR ($CDCl_3$) δ 13.6 (broad, 1, OH), 7.62–7.06 (m, 8, aromatic H), 4.28 (broad, 2, CH_2), 2.62 (s, 3, $COCH_3$), 2.24 (s, 3, =CCH_3); mass spectrum m/e 352 (M^+).

Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.08; H, 4.86; Cl, 10.05; N, 7.94. Found: C, 67.82; H, 4.92; Cl, 10.06; N, 8.11.

Fractions 9–11 (ca. 0.8 g) were crystallized from ethyl acetate to give 0.278 g of **7**: mp 276–277 °C, raised on recrystallization to 278–279 °C dec; uv λ_{max} 209 nm (ε 27 500), 248 (63 000), 280 (22 500), sh 319 (7500), 333 (1210), 355 (10 000), 369 (8850); ir NH 3320; C=O/C=N 1640, 1630; C=N/C=C 1600, 1570, 1540, 1500; C–N 1300, 1160, 950; aromatic 820, 710 cm^{-1}; NMR (Me_2SO-d_6) δ 11.8 (broad, 1, NH), 8.07 (d, 1, aromatic H, J = 9.8 Hz), 7.8–7.43 (m, 7, aromatic H), 2.93 (s, 3, $COCH_3$), 2.74 (s, 3, NC–CH_3); mass spectrum m/e 334 (M^+).

Anal. Calcd for $C_{20}H_{15}ClN_2O$: C, 71.75; H, 4.52; Cl, 10.59; N, 8.37. Found: C, 71.74; H, 4.76; Cl, 10.48; N, 8.20.

Fraction 12 (0.398 g) was discarded. Fractions 13–14 (0.645 g) were crystallized from ether to give 0.179 g of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, mp 213–214 °C. It was identical with an authentic sample[13c] as shown by mixture melting point and TLC.

7-Chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinoline-3-carboxylic Acid (8). The solid *tert*-butyl ester **6** (3.2 g, 8.17 mmol) was placed in a flask, cooled in ice, 62 ml of trifluoroacetic acid was added, and the mixture was allowed to stand at room temperature for 30 min. It was evaporated in vacuo (ca. 0.1 mm) at 30 °C and 100

ml of saturated aqueous sodium bicarbonate solution was added. The mixture was shaken; the resulting suspension filtered and the solid washed with water, then ether. Crystallization from CH_3OH–$CHCl_3$ gave 1.9 g of yellow needles, mp 296–297 °C dec. Second crop: 0.45 g; mp 295–296 °C; uv λ_{max} 204 nm (ϵ 31 500), sh 236 (39 550), 251 (56 800), 332 (12 850), 358 (9000), sh 372 (8100); ir NH/acid OH 3140 (broad), 3050, 2760, sh 2700; C=O 1700; C=C/C=N 1625, 1600, 1565; C–O/C–N 1290, 1175, 1165, 1135, 1075; aromatic 825, 775, 725, 700 cm^{-1}; NMR (Me_2SO-d_6) was poor owing to low solubility; mass spectrum *m/e* 336 (M^+).

Anal. Calcd for $C_{19}H_{13}ClN_2O_2$: C, 67.76; H, 3.89; Cl, 10.57; N, 8.32. Found: C, 67.48; H, 3.89; Cl, 10.78; N, 8.32.

Ethyl Ester of 7-Chloro-1-[3-(dimethylamino)propyl]-2-methyl-9-phenyl-1*H*-[3,2-*b*]quinoline-3-carboxylic Acid. Sodium hydride (0.421 g of 57% dispersion in mineral oil, 0.01 mol) was added to a solution of **5** (3.64 g, 0.01 mol) in 50 ml of DMF and the mixture was heated for 40 min at 95 °C. A solution of 3-dimethylaminopropyl chloride (1.21 g, 0.01 mol) in 1.21 g of xylene was added during 3 min, and heating continued overnight. The mixture was evaporated, H_2O and CH_2Cl_2 added, and the organic layer was shaken with aqueous 10% HCl. Since the resulting oily hydrochloride was not suitable for workup, the mixture was brought to pH 10 with 5% aqueous NaOH, the organic layer was separated, washed with saturated salt solution, dried ($MgSO_4$), and evaporated. The residue (3.3 g) was extracted with boiling ether (4 × 50 ml) and the extract concentrated to 25 ml to give 0.993 g of the product: mp 177–178 °C, raised to 179.5–180.5 °C on two recrystallizations from ether; uv sh 230 nm (ϵ 28 300), λ_{max} 256 (64 650), sh 322 (6500), 336 (11 950), 357 (9350), sh 370 (8200); ir *N*-alkyl 2810, 2780, 2760, 2720; C=O 1670; C=C/C=N 1610, 1590, 1545, 1485; C–O/C–N 1265, 1225, 1170, 1120, 1100; aromatic 830, 710 cm^{-1}; NMR ($CDCl_3$) δ 8.24 (d, 1, aromatic H, J = 8.5 Hz), 7.71–7.6 (m, 7, aromatic H), 4.54 (q, 2, OCH_2, J = 7 Hz), 3.85–3.5 (m, 2, *N*-pyrrole CH_2), 2.86 (s, 3, NC–CH_3), 2.06 [s, 6, $N(CH_3)_2$], 1.52 (t, 3, OC–CH_3), 1.76–1.25 (m, 4, CH_2CH_2N dialkyl); mass spectrum *m/e* 449 (M^+).

Anal. Calcd for $C_{26}H_{28}ClN_3O_2$: C, 69.40; H, 6.27; Cl, 7.88; N, 9.34. Found: C, 68.99; H, 6.34; Cl, 7.97; N, 9.19.

The residue from the original ether extraction and filtrates from the crystallization were combined and evaporated and the residue (2.5 g) chromatographed on 250 g of silica gel using 10% CH_3OH–$CHCl_3$. Fractions 1–3 (500 ml total) gave 0.5 g of starting material. Fraction 7 gave a mixture (discarded). Fractions 8–11 gave 1.4 g of the product. Crystallization from ether gave 0.943 g, mp 179–180 °C.

Synthesis of Compound 10.[14] A. Reaction of 2-Amino-5-chlorobenzophenone with Ethyl Acetoacetate. A mixture of 2-amino-5-chlorobenzophenone (23.2 g, 0.1 mol) and ethyl acetoacetate (52 g, 0.4 mol) was heated at 150–155 °C (oil bath temperature) for 3 h using a take-off condenser (15 ml was collected). The resulting suspension was cooled and the product filtered and washed with ether: 24 g (81% yield); mp 274–275 °C unchanged on crystallization from CH_2Cl_2; uv λ_{max} 207 nm (ϵ 35 450), 237 (39 400), 277 (6200), sh 330 (4400), 344 (5900), sh 356 (5250); ir =CH,NH,OH 3140, 2900 broad, 2730; C=O,C=N,C=C 1710 m, 1640 s, 1595, 1575, 1550; C–N/C–O 1405, 1350, 1085, 1080; aromatic 770, 710, 665 cm^{-1}; NMR (Me_2SO-d_6) δ 12.5 (broad, exchangeable with D_2O), 7.76–7.25 (m, 7, aromatic H), 7.0 (d, 1, aromatic H, J = 2.2 Hz), 2.25 (s, 3, CH_3); mass spectrum *m/e* 297 (M^+).

Anal. Calcd for $C_{17}H_{12}ClNO_2$: C, 68.56; H, 4.06; Cl, 11.91; N, 4.71. Found: C, 68.21; H, 4.10; Cl, 11.80; N, 4.80.

B. Reaction of 2-Amino-5-chlorobenzophenone with *tert*-butyl Acetoacetate. A mixture of 2-amino-5-chlorobenzophenone (4.61 g, 0.02 mol) and 46 ml of *tert*-butyl acetoacetate was refluxed for 2 h. The resulting suspension was filtered and the product washed with ether, 4.1 g (68% yield), mp 273.5–275 °C, raised to 274–275 °C on recrystallization from CH_2Cl_2. This compound was identical with the product obtained by condensation of 2-amino-5-chlorobenzophenone with ethyl acetoacetate as shown by comparison of TLC, uv, ir, NMR, and mass spectra.

Synthesis of 11. Sodium hydride (0.841 g of 57% dispersion in mineral oil, 0.02 mol) was added to a solution of **10** (5.94 g, 0.02 mol) in 100 ml of DMF and the mixture was heated at 95 °C for 30 min. A solution of 2-dimethylaminoethyl chloride (2.14 g, 0.02 mol) in 2.14 g of xylene was added, and heating continued for 18 h. The mixture was evaporated, H_2O and CH_2Cl_2 added, and the organic layer shaken with 10% aqueous HCl (ether added to break up emulsion). The resulting oily layer was separated by decantation, washed with CH_2Cl_2–ether (1:1), cooled, and basified. The product was extracted with CH_2Cl_2, and the solution washed with saturated salt solution, dried ($MgSO_4$), and evaporated. The residue was crystallized from ether to give 2.8 g: mp 155–156 °C, raised to 156–157 °C on recrystallization; uv λ_{max} 209 nm (ϵ 33 100), 239 (41 400), 282 (6200), sh 330 (4150), 345 (5750), sh 358 (4900); ir *N*-alkyl 2740; C=O 1705; C=O or C=N 1630; C=C 1600, 1585, 1555, 1485; C–N 1310, 1155, 1105; aromatic 810, 705 cm^{-1}; NMR ($CDCl_3$) δ 7.62–7.16 (m, 8, aromatic H), 4.48 (apparent t, 2, $CONCH_2$, apparent J = 7.5 Hz), 2.69 (apparent t, 2, CH_2N dialkyl, apparent J = 7.5 Hz), 2.4 (s, 3, $COCH_3$); mass spectrum *m/e* 368 (M^+).

Anal. Calcd for $C_{21}H_{21}ClN_2O_2$: C, 68.38; H, 5.74; Cl, 9.61; N, 7.60. Found: C, 68.30; H, 5.76; Cl, 9.83; N, 7.66.

***N*-Acetonyl-*N*-acetylacetamide** was prepared from glycine as described in the literature.[7] One distillation gave the product, bp 101–104 °C (0.08 mm). VPC indicated ca. 90% purity; NMR showed the presence of some *N*-acetonylacetamide.

***N*-Acetonylacetamide** was prepared by aqueous hydrolysis of *N*-acetonyl-*N*-acetylacetamide as described in the literature.[7] The product boiled at 103 °C (0.7 mm); VPC 98.98%; ir, mass spectrum were in accord; NMR ($CDCl_3$) δ 6.48 (broad, 1, NH), 4.18 (d, 2, CH_2, J = 5 Hz), 2.22 (s, 3, $NCOCH_3$), 2.05 (s, 3, C–$COCH_3$).

Reaction of 2-Amino-5-chlorobenzophenone with *N*-Acetonylacetamide. A mixture of 2-amino-5-chlorobenzophenone (11.9 g, 0.0515 mol) and *N*-acetonylacetamide (23.8 g, 0.206 mol) was heated at 170 °C (oil bath temperature) for 4 h using a take-off condenser (1.1 ml was collected). The residue was chromatographed on 2 kg of silica gel using 5% MeOH–$CHCl_3$. Fractions 1–9 (3.85 l. total) gave no material. Fractions 10–14 (250 ml each from now on) gave a trace of oil. Fractions 15–17 gave 2.8 g of *N*-[(6-chloro-4-phenyl-2-quinolyl)methyl]acetamide (**16**), which was crystallized from CH_3OH: 2.3 g, mp 167.5–168.5 °C; uv λ_{max} 234 nm (ϵ 50 500), 290 (8000), sh 310 (5420), 325 (4460); ir NH=CH 3320, 3060; C=O 1645; C=C/C=N 1590, 1570, 1540, 1485; C–N 1355, 1345, 1290, 1030; aromatic 835, 765, 715, 710 cm^{-1}; NMR ($CDCl_3$) δ 8.13–7.39 (m, 8, aromatic H), 7.24 (s, 1, C_3H), ~7.24 (broad, 1, NH), 4.71 (d, 2, CH_2, J = 5 Hz), 2.12 (s, 3, CH_3); mass spectrum *m/e* 310 (M^+).

Anal. Calcd for $C_{18}H_{15}ClN_2O$: C, 69.56; H, 4.87; Cl, 11.41; N, 9.02. Found: C, 69.63; H, 4.97; Cl, 11.48; N, 9.13.

Fractions 18–21 gave 1.9 g of a mixture. Fractions 22–72 gave 8.6 g of *N*-(6-chloro-2-methyl-4-phenyl-3-quinolyl)acetamide (**15a**), which was crystallized from MeOH, 6.7 g, mp 181–182 °C. Second crop: 1.3 g, mp 178–180 °C; uv sh 210 nm (ϵ 31 750), λ_{max} 233 (45 950), 282 (5850), sh 296 (5000), 311 (4100), 326 (4300); ir NH 3250; C=O/amide II 1655, 1605, 1585, 1570, 1560, 1505, 1480; C–N 1275, 1270, 1040; aromatic 840, 710 cm^{-1}; NMR ($CDCl_3$) δ 8.05–7.08 (m, 9, aromatic H and NH), 2.64 (s, 3, N=CCH_3), 1.88 (s, 3, $COCH_3$); mass spectrum *m/e* 310 (M^+).

Anal. Calcd for $C_{18}H_{15}ClN_2O$: C, 69.56; H, 4.87; Cl, 11.41; N, 9.02. Found: C, 69.70; H, 5.05; Cl, 11.51; N, 9.23.

3-Amino-6-chloro-2-methyl-4-phenylquinoline (15b). A mixture of **15a** (1.02 g, 3 mmol), sodamide (0.82 g, 21 mmol), and 10 ml of freshly distilled *N,N*-diethylaniline was refluxed for 1.75 h. A lightly colored suspension resulted. It was cooled in ice, 10 ml of H_2O was added, and after stirring for 15 min, the mixture was extracted with ether (4 × 25 ml). The organic solution was washed with saturated salt solution, dried ($MgSO_4$), and evaporated, toward the end at 0.1 mm and 95 °C, to give 0.9 g. Crystallization from ether gave 0.298 g of recovered starting material. The filtrate was evaporated and the residue chromatographed on 60 g of silica gel using 5% MeOH–$CHCl_3$. Fractions 1–4 (200 ml total) gave no material. Fractions 5–6 (10 ml from now on) gave 0.205 g of diethylaniline. Fractions 7–8 gave 0.23 g of **15b.** Crystallization from ether gave 90 mg, mp 141–142 °C. Second crop: 130 mg, mp 140–141 °C; uv λ_{max} 206 nm (ϵ 24 900), 219 (26 800), 249 (42 800), sh 279 (5350), sh 290 (4300), sh 302 (2870), 349 (6860); ir NH 3460, 3360; NH def, C=C,C=N 1625, 1605, 1585, 1505, 1490; aromatic 875, 820, 715 cm^{-1}; NMR ($CDCl_3$) δ 8.0–7.17 (m, 8, aromatic H), 3.78 (broad s, 2, NH_2, exchanges with D_2O), 2.65 (s, 3, CH_3); mass spectrum *m/e* 268 (M^+).

Anal. Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.87; Cl, 13.19; N, 10.43. Found: C, 71.44; H, 4.90; Cl, 13.29; N, 10.34.

***N*-(6-Chloro-2-methyl-4-phenyl-3-quinolyl)diacetamide (15c).** A mixture of **15a** (2 g, 6.45 mmol) and 5 ml of acetic anhydride was refluxed for 19 h. The resulting solution was allowed to crystallize. The product was recrystallized from ether to give 1.68 g of **15c:** mp 160–161 °C; uv sh 216 nm (ϵ 40 250), λ_{max} 235 (54 450), 281 (5850), sh 300 (4300), 314 (3850), 328 (4500); ir C=O 1725, 1695; C=C/C=N 1610, 1580, 1560, 1480; C–N 1280, 1265, 1230, 1020; aromatic 835, 715 cm^{-1}; NMR ($CDCl_3$) δ 8.18–7.0 (m, 8, aromatic H), 2.6 (s, 3, N=CCH_3), 2.15 (s, 6, 2 $COCH_3$); mass spectrum *m/e* 352 (M^+).

Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.08; H, 4.86; Cl, 10.05; N, 7.94. Found: C, 68.43; H, 4.93; Cl, 10.05; N, 7.94.

***N*-(6-Chloro-2-methyl-4-phenyl-3-quinolyl)acetamide 1-Oxide.** A solution of **15a** 5.25 g, 0.017 mol) and *m*-chloroperbenzoic

acid (85%, 3.45 g, 0.017 mol) in 75 ml of CH_2Cl_2 was stirred at room temperature for 6 h. The resulting suspension was filtered and the solid washed with saturated $NaHCO_3$ solution. The filtrate was separated, and the organic layer was washed with $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was combined with the above solid and crystallized from MeOH: 4.63 g, mp 257–258 °C, raised to 259–260 °C on recrystallization; uv sh 224 nm (ϵ 26 300), λ_{max} 236 (32 100), 252 (35 250), 331 (10 900); ir NH=CH 3150, 3080, 2770; C=O 1685; C=C/C=N amide II 1600, 1585, 1560, 1515, 1500, 1480; C–N/N–O 1330, 1265, 1205, 1175, 1105; aromatic 830, 710 cm^{-1}; NMR (Me_2SO-d_6) δ 7.94–7.22 (m, 8, aromatic H), ~3.24 (broad, 1, NH), 2.49 (s, 3, N=CCH_3), 1.85 (s, 3, $COCH_3$); mass spectrum *m/e* 326 (M^+).

Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; Cl, 10.85; N, 8.57. Found: C, 65.91; H, 4.71; Cl, 10.85; N, 8.57.

X-Ray Structure Determination of the 1-[3-(Dimethylamino)propyl] Derivative of 5. A. Crystal Data. The crystals are triclinic, clear prisms; space group $P\bar{1}$; a = 10.597 (2) Å; b = 11.402 (1) Å; c = 19.810 (1) Å; α = 91.08 (1)°; β = 93.99 (1)°; γ = 90.11 (2)°; V = 2387.6 (4) Å^3; Z = 4; ρ_{calcd} = 1.25 g/cm^3. Cell parameters were calculated by least squares from accurately determined Kα_1 2θ values for 19 selected high angle reflections.

Intensity data were collected on a Syntex $P\bar{1}$ diffractometer controlled by an IBM 1800 computer. The θ–2θ scan technique was used with graphite-monochromatized Cu Kα radiation. A 2θ range of 3° was scanned at a variable rate (4–10° per minute) depending on the intensity of the reflection being measured. The total time spent counting background—half at each end of the scan—was equal to the time spent scanning. The crystal orientation was determined by the computer before data collection using seven orienting reflections. Data were limited to 2θ less than 100° because crystal quality was not very good (in the range 2θ = 90–100°, the mean $I/\sigma(I)$ was only 1.7). Ten reflections were monitored periodically during the data collection; a slight loss in intensity (4%) was noted. Standard deviations in observed intensities were approximated by the function $\sigma(I) = [\sigma^2(I)\ \textit{counting statistics} + (0.019\ I)^2]^{1/2}$ where the coefficient of I in the last term was calculated from those deviations in the check reflection observations (after deterioration correction) which were not explained by counting statistics. The usual Lorentz correction was applied[15] along with a polarization correction appropriate for a monochromator with 50% perfect character.[16] The final reduced set (4914 reflections) contained a large number of very weak reflections, including 655 which are negative intensity observations (scaled background counts exceeded scan counts).

B. Trial Solution. A trial solution was obtained by direct methods,[17] with some effort, using the DIREC program written by one of the authors (D.J.D.). The 19th E map phased by this automatic program clearly showed 41 of the 64 nonhydrogen atoms; the rest were easily found by tangent formula extension of phases of structure factors calculated from these trial atoms. The successful E map was calculated with phases from an extension of the seventh highest ranking set of phases from the third symbolic addition (reflections $\bar{3},2,0$; $3,3,\bar{6}$; and $\bar{2},1,1$ were used to define the origin, and reflections $\bar{2},2,0$; $\bar{3},1,\bar{2}$; $\bar{2},1,\bar{1}$; $4,1,\bar{1}0$; and $\bar{5},1,16$ were assigned symbolic phases).

C. Refinement. Coordinates, thermal parameters, and the scale factor were refined by multiple-matrix least squares. The function minimized was $\Sigma w(F_o^2 - F_c^2)^2$.

Weights w were taken equal to the reciprocals of the variances $\sigma^2(F_o^2)$ determined at data reduction time and scaled by propagation of error through subsequent corrections. All reflections were used in the refinement regardless of size. Reflections with negative observed intensity were used in the refinement as negative $|F_o|^2$. Atomic form factors are from International Tables for X-Ray Crystallography,[18] except for hydrogen, which was taken from Stewart, Davidson, and Simpson.[19]

The symmetry-independent molecules have a pseudosymmetric relationship (which holds to within 0.8 Å), of $1-x, \frac{1}{2}-y, -\frac{1}{2}+z$. If this relationship were exact, the space group would be $P2_1/b$. In the matrix scheme for the final refinement, coordinates were in two matrices, with like parts of each molecule in the same matrix (because of pseudosymmetric correlations). The scale factor and the anisotropic thermal parameters of the chlorines were in another matrix, and the remainder of the anisotropic thermal parameters were in individual (6 × 6) block matrices. Hydrogen parameters were not refined, but were added to structure factor calculations. Positions for the C(21) methyl hydrogens were found in a difference Fourier map. Coordinates for the other hydrogen atoms were calculated assuming standard (tetrahedral or planar) orientations. Hydrogen isotropic temperature factors were fixed about ½ unit higher than attached carbons. The dimethylamino group in the primed molecule appears to be disordered, since atoms in this region refined to coordinates with unreasonable distances and angles and thermal parameters with largest principal axes from 0.6 to 0.9 Å. An effort was made to find a model for the disorder. A difference Fourier map, with C12′–C15′ out of the calculations, showed large peaks at chemically reasonable positions, but no reasonable alternate model using the smaller peaks. Upon refinement, the dimethylamino atoms moved back to their original locations. A difference Fourier map with all atoms in the structure factor calculations showed no extraneous peaks of larger size than hydrogens. Refinement was considered converged when all shifts were less than ¼ standard deviations, except for parameters of the dimethylamino group in the primed molecule where some shifts were as large as standard deviations.

The final agreement indices for all 4914 reflections are $R = 0.123$ ($R = \Sigma||F_o| - |F_d||/\Sigma|F_o|$); weighted $R = [\Sigma w(|F_o|^2 - |F_d|^2)^2/\Sigma w|F_o|^4]^{1/2} = 0.128$; and standard deviation of fit = $[\Sigma w(|F_o|^2 - |F_d|^2)^2/(m-s)]^{1/2} = 1.66$. For the 1471 reflections with F_o^2 greater than 3 standard deviations, R is 0.048 and weighted R is 0.097.

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Registry No.—**4,** 7564-07-0; **5,** 58375-02-3; **5** 1-(3-dimethylaminopropyl) derivative, 58375-03-4; **6,** 58375-04-5; **7,** 58375-05-6; **8,** 58375-06-7; **9,** 58375-07-8; **10,** 58375-08-9; **11a,** 58375-09-0; **11b,** 58375-15-8; **15a,** 58375-10-3; **15b,** 58375-11-4; **15c,** 58375-12-5; **16,** 58375-13-6; ethyl acetoacetate, 141-97-9; *tert*-butyl acetoacetate, 1694-31-1; acetylacetone, 123-54-6; 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, 1694-78-6; 3-dimethylaminopropyl chloride, 109-54-6; 2-amino-5-chlorobenzophenone, 719-59-5; *N*-acetonyl-*N*-acetylacetamide, 51862-97-6; *N*-acetonylacetamide, 7737-16-8; *N*-(6-chloro-2-methyl-4-phenyl-3-quinolyl)acetamide 1-oxide, 58375-14-7.

Supplementary Material Available. Tables of H atom coordinates and anisotropic temperature factors (2 pages). Ordering information is given on any current masthead page.

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