eluent. The faster moving fraction gave, after recrystallization from ether–petroleum ether, 215 mg (36%) of epoxide **12a** as white needles: mp 82.5–83.0 °C; IR (CH_2Cl_2) 1795 (β-lactam), 1760 (ester) cm^{-1}; NMR ($CDCl_3$) δ 1.50, 1.65 (s and d, J = 5 Hz, 9 H, 2-CH_3 and epoxide CH_3), 3.35–3.62 (q, 1 H, J = 5 Hz, epoxide H), 4.65 (s, 1 H, H-3), 4.8 (s, 2 H, CH_2CCl_3), 5.25 (s, 1 H, H-5); *m/e* 374 (M^+, calcd for $C_{12}H_{14}NO_4Cl_3S$, 374).

Anal. Calcd for $C_{12}H_{14}NO_4Cl_3S$: C, 38.47; H, 3.77; N, 3.74; Cl, 28.39; S, 8.56. Found: C, 38.52; H, 3.77; N, 3.70; Cl, 28.19; S, 8.34.

The reaction was repeated at 25 °C. An NMR ($CDCl_3$) spectrum of the residue after evaporation of the solvent contained all the previously listed signals of **12a** plus the following: δ 2.38 and 2.40 (s, acetyl groups of **13a** and **14a**), 4.38, 5.63 (2d, J = 2 Hz, *trans*-β-lactam protons of **13a**), 4.60, 5.42 (2d, J = 4 Hz, *cis*-β-lactam protons of **14a**), 4.42, 4.60 (2 s, H-3 of **13a** and **14a**). Absorptions by the C_2-methyl groups and the methylene protons superimposed on the respective epoxide signals.

The residue was chromatographed on silica gel using ether–methylene chloride (1:50) as eluent. The first fraction gave 60 mg (20%) of **12a.**

Later fractions after evaporation and crystallization from methylene chloride–petroleum ether gave 90 mg (30%) of **15a** as white needles: mp 118 °C; IR ($CHCl_2$) 1760, 1675, 1575 (C = 0, ester) cm^{-1}; NMR ($CDCl_3$) 1.63 (s, 6 H, 2-CH_3), 2.42 (s, 3 H, acetyl), 4.60 (d, 1 H, J = 5 Hz, H-3, sharpens with D_2O), 4.81 (s, 2 H, CH_2CCl_3), 7.05–7.50 (br m, 1 H, NH, exchange with D_2O), 8.05 (d, 1 H, J = 9 Hz, sharpens with D_2O).

Reaction of 1 with Phenylacetaldehyde. Phenylacetaldehyde (81 mg, 0.68 mmol) was reacted with ester **1** (243 mg, 0.68 mmol) under the same conditions (0 °C) as described above for the reaction with acetaldehyde. The fastest moving fraction contained unreacted phenylacetaldehyde. Later fractions gave 40 mg of epoxide **12b** (36%) as yellow needles. Analytical samples were obtained after several recrystallizations from ether–petroleum ether as white needles: mp 119–120 °C; IR (CH_2Cl_2) 1800 (β-lactam), 1775 (ester) cm^{-1}; NMR ($CDCl_3$) δ 1.31, 1.46 (2 s, 6 H, 2-CH_3), 2.81–3.78 (m, 3 H, epoxide H and CH_2Ph), 4.62 (s, 1 H, H-3), 4.75 (s, 2 H, CH_2CCl_3), 5.55 (s, 1 H, H-5), 7.26 (m, 5 H, Ph).

Anal. Calcd for $C_{18}H_{18}NO_4Cl_3S$: C, 47.96; H, 4.02, N, 3.11; Cl, 23.59; S, 7.11. Found: C, 47.96; H, 4.05; N, 3.03; Cl, 23.49; S, 7.06.

Acknowledgment. This research was supported by a grant from the Sloan Basic Research Fund and by A. H. Robins, Co., Richmond, Va. We are grateful to Dr. A. L. Demain and Miss N. Hunt of the Department of Food and Nutrition for bioassays.

Registry No.—**1,** 51056-24-7; **2a,** 67760-93-4; **2b,** 67760-94-5; **2c,** 67760-95-6; **2d,** 67760-96-7; **3a,** 67814-36-2; **3b,** 67814-37-3; **3c,** 67814-38-4; **4,** 63784-22-5; **5,** 63784-23-6; **6,** 67760-97-8; **7,** 67760-98-9; **8,** 67814-39-5; **9,** 67814-40-8; **12a,** 67760-99-0; **12b,** 67761-00-6; **13a,** 67761-01-7; **14a,** 67761-02-8; **15a,** 67761-03-9; acrylonitrile, 107-13-1; ethyl acrylate, 140-88-5; *tert*-butyl acrylate, 1663-39-4; phenol, 108-95-2; diphenyldiazomethane, 883-40-9; acetaldehyde, 75-07-0; phenylacetaldehyde, 122-78-1.

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Chloroacetamide Photocyclization of Indole Derivatives. Synthesis, Stereochemistry, and Crystal Structure of 3,7-Methano-3-azacycloundecino[5,4-*b*]indole (Deethylquebrachamine) Derivatives

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Condensation of 3-(lithiomethyl)pyridine with ethyl indole-2-carboxylate or the 1-methyl or 5-methoxy derivatives yields the corresponding substituted 2-indolyl (3-pyridyl)methyl ketone. Catalytic reduction, chloroacetylation, and ketalization with ethylene glycol yield the dioxolane derivatives of the corresponding substituted 2-indolyl [1-(chloroacetyl)piperidin-3-yl]methyl ketone. These are photocyclized to substituted 3,7-methano-3-azacycloundecino[5,4-*b*]indoles, which contain the skeletal framework of the quebrachamine family of indole alkaloids. NMR data and a crystal structure of the 1-methyl compound (**8b**) establish that the principal photoproducts possess an unstable conformational structure. Thermal conversion to the stable atropisomeric structure occurs at 140 °C. The stable atropisomers are minor products of the photocyclization. In the 5-methoxy system an alternative pathway for photocyclization at C-7 of the indole ring is observed to a small extent and the crystal structure of this photoproduct (**12c**) is reported.

The photolysis of chloroacetamidoalkylindoles leads to cyclization,[2] and independent studies in our laboratory[3] and by Snieckus and co-workers[4] have demonstrated that the reaction has utility for the synthesis of polycyclic indole derivatives containing medium-sized rings. The present paper describes the application of this method to the synthesis of the ring system found in indole alkaloids such as quebrachamine and cleavamine, the products of acid-catalyzed cleavage of the dimeric *vinca* indole alkaloids. The latter structural family has been the focus of considerable synthetic

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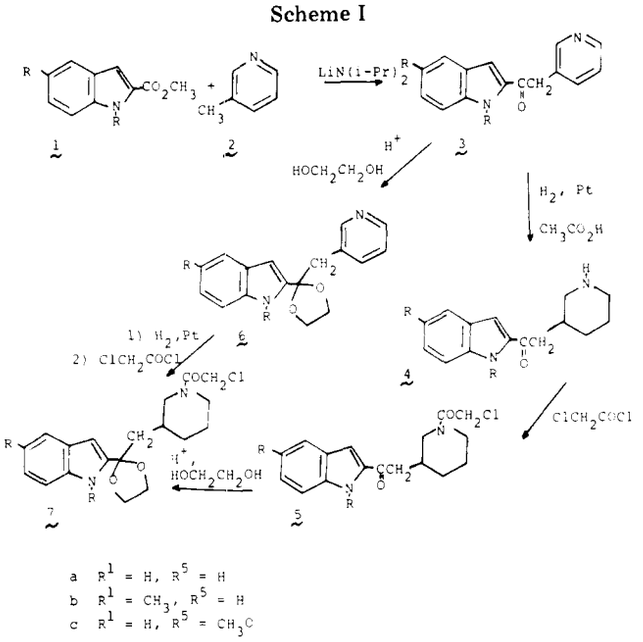
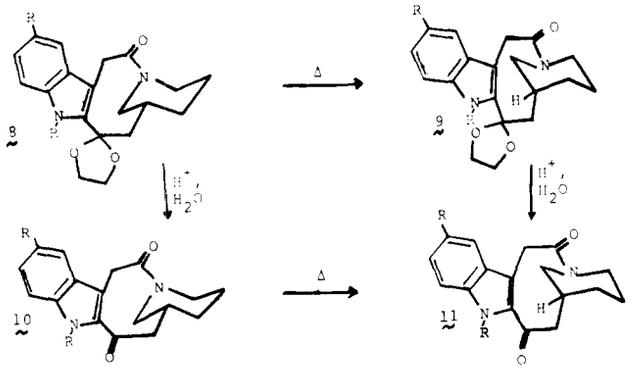
Scheme I



interest because of the importance of these alkaloids in cancer chemotherapy.[5] One of the systems discussed here has previously been described briefly with regard to the stereochemistry of the photocyclization.[6]

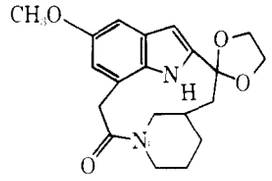
Synthesis. The synthesis of the requisite starting materials is outlined in Scheme I. It is similar to that used earlier,[3] but difficulties in the ketalization of 2-indolyl (3-pyridyl)methyl ketones **3a** and **3c** led to utilization of the sequence **3** → **4** → **5** → **7** as the preferred route to **7a–c.** We, like Kaiser and Petty,[7] found lithium diisopropylamide to be the most satisfactory base for preparation of (3-pyridyl)methyllithium, but satisfactory results were achieved without the use of hexamethylphosphoramide. The other steps in the synthesis of chloroacetamides **7a–c** require no special comment.

The desired photocyclization products were isolated in ~50% yield in the case of **8a** and **8c,** but the yield was lower (~35%) for the *N*-methyl derivative **8b.** Each major photoproduct was accompanied by a small amount of an isomeric compound (**9a–c**). Refluxing **8a–c** in xylene resulted in clean



conversion to the minor photoproduct **9a–c** in each case. In the previous study[3] we had concluded that photocyclization led to atropisomeric structures related to the two possible chair conformations of the piperidine ring in the starting material. A similar explanation accounts for the spectral properties of the isomeric compounds prepared in this study. Thus, the atropisomeric structures of **8a–c** and **9a–c** are related by a conformational change which occurs with a $t_{1/2}$ in the range of hours at ~140 °C in xylene. The barrier to the conformational change results from the steric repulsion arising as the piperidine methylene group passes through the nine-membered ring. Each pair of stable and unstable ketals can be hydrolyzed to a corresponding pair of atropisomeric keto lactams. The NMR spectral data permit assignment of the atropisomeric structures as discussed below, and these conclusions have been confirmed by a single-crystal structure determination in the case of **8b.**

A third photoproduct was isolated from photolysis of **7c.** Its structure has been shown by X-ray diffraction to be **12c,**



12c

the product of photocyclization at the 7 position of the indole ring.

NMR Studies. The series of compounds **8b–11b** was examined at 250 MHz, while the series **8a–11a** and **8c–11c** were studied at 90 or 100 MHz. It was, in general, possible to identify signals corresponding to the protons adjacent to nitrogen in the piperidine ring. In many cases geminal relationships were confirmed by decoupling experiments. The data are summarized in Table I.

The thermally unstable atropisomers of the **8** and **10** series consistently reveal a doublet of doublets (J = ~14 and ~10 Hz) at δ 2.7 ± 0.2. This proton is coupled by 14 ± 1 Hz to the geminal equatorial proton. The second coupling of about 10 Hz is consistent with structures **8** and **10** since the axial proton at C(10) would experience an axial–axial coupling with the axial proton at C(7). In contrast, in the **9** and **11** series the corresponding signal is a doublet (with some small coupling in certain cases). The vicinal axial–equatorial coupling space is small, as expected.[8]

UV and IR Spectra. The 2-acylindoles **10a–c** show evidence of the strain present in the C-ring by their ultraviolet spectra. While **11a** and **11b** reveal typical 2-acylindole absorption at 310–315 nm and **11c** shows a similar spectrum shifted somewhat toward longer wavelength by the effect of the methoxy group, the spectra of **10a–c** are atypical. A very broad band between 260 and 310 nm is observed, showing some additional structure in the case of **10a** and **10c.** These spectra indicate that the conjugation of the indole ring and carbonyl group is disrupted by the twisting caused by the geometric requirements of the strained ring system.

The infrared spectra also provide evidence for weakened conjugation in the **10** series of keto lactams. The **11** series shows the normal effect of conjugation of the ketonic carbonyl group with the indole ring in that the carbonyl frequency is below 1650 cm^{-1}. Each of the compounds in the **10** series has a ketone carbonyl absorption near 1690 cm^{-1}.

Crystal Structure of 8b. The molecular structure and stereochemistry of **8b** were confirmed by direct single-crystal X-ray analysis of its hemihydrate. The asymmetric unit of the crystal contains two chemically equivalent but crystallographically independent molecules (A and B), linked by hydrogen bonding through a single molecule of water of hydration. Atomic parameters defining the crystal structure are given in the supplementary material. A stereoscopic view[9] of one of the two molecules (A) is shown in Figure 1, and mean bond lengths and angles are shown in Figure 2.[10] A comparison of chemically equivalent bond lengths and angles in the two molecules gives root mean square deviations from the mean values of 0.004 Å and 0.45°, so that there is good agreement between corresponding dimensions in the two molecules.[11]

The two molecules differ in the conformation of the dioxolane ring. In molecule A this ring has an envelope conformation ($\bar{\Delta}$ = −29°), whereas in molecule B it has a half-chair conformation ($\bar{\Delta}$ = −2°).[12]

Table I. NMR Signals [a]

compd	C-10 eq	C-10 ax	C-4 eq	C-4 ax	compd	C-10 eq	C-10 ax	C-4 eq	C-4 ax
8a	5.07 (d)	2.58 (d of d)	?	?	**9a**	*5.15* (d)	*3.13* (d)	*4.48* (d)	*2.58* (m)
8b	*5.25* (d)	*2.52* (d of d)	*4.25* (d of d)	*2.80* (t of d)	**9b**	*5.12* (d)	*3.08* (d)	?	?
8c	*5.06* (d)	*2.64* (d of d)	~4.3 (d)	?	**9c**	5.13 (d)	3.35 (d)	4.57 (d)	?
10a	4.28	~2.90 (m)	3.90 (d)	~2.90 (m)	**11a**	*4.02* (d)	*3.30* (m)	*4.65* (d)	*2.65* (t of d)
10b	*4.40* (d)	*2.76* (d of d)	3.86 (d of d)	?	**11b**	3.90 (d)	?	*4.35* (d)	*2.76* (m)
10c	4.42 (d)	2.90 (d of d)	?	?	**11c**	4.07 (d)	?	4.67 (d)	2.67 (t of d)

[a] Given in δ units. Italicized numbers indicate geminal relationship confirmed by decoupling. The numbering scheme is that used in the crystal structure in Figure 2.

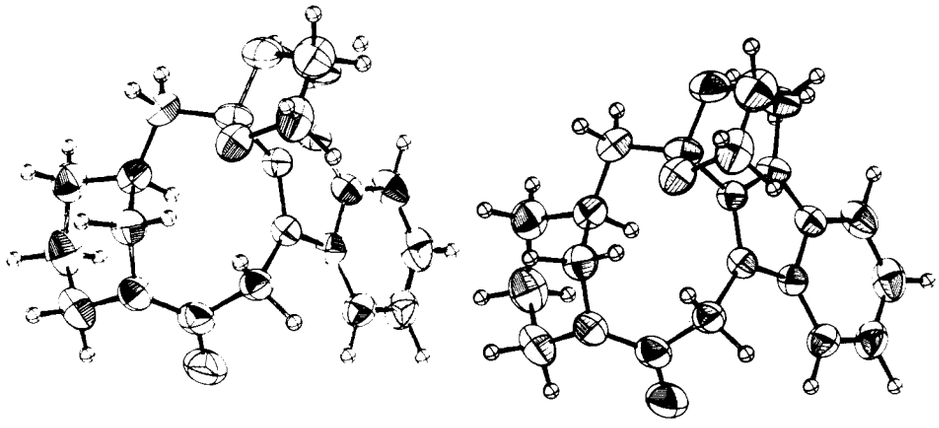


Figure 1.

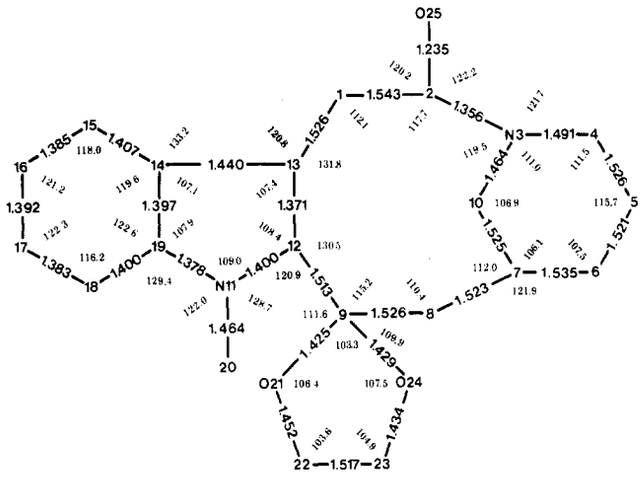


Figure 2.

The mean C_{sp^3}–C_{sp^3} and aromatic C–C bond lengths are normal, but the mean C(2)–N(3) bond length (1.356 Å) is longer than is normally found in amides (1.322 Å).[13] In both molecules A and B, the four atom grouping about the amide carbon, C(2), is planar.[14]

Within limits of error, the individual five- and six-membered rings of both indole rings are planar. While the entire indole ring is planar in molecule A, there is some deviation in molecule B. For the indole ring in molecule B the maximum and mean displacements from the least-squares plane are 0.035 and 0.019 Å, respectively. The *N*-methyl group, C(20), in molecule B is displaced by 0.210 Å from the ring plane. This displacement may be related to the conformation of the dioxolane ring since there would be an unacceptably short C(20)···O(21) separation in B if the methyl group was not displaced from planarity.

There are short transannular contacts involving O(24) of the dioxolane ring and hydrogen atoms of the lactam ring. In molecule A, O(24)···H(1b) is 2.43 Å and O(24)···H(10a) is 2.06 Å, whereas the corresponding distances in molecule B are 2.43 and 2.02 Å.

Molecules A and B seem to be linked by hydrogen bonds from the molecule of water of hydration to the carboxyl oxygen atoms. Although the hydrogen atoms attached to the water molecule could not be found from difference electron density maps, the angle O(25)···H_2O···O(25) is 125.7° and the O···O distances are 2.804 Å to A and 2.818 Å to B.

Significant differences in functionality and substitution pattern preclude detailed comparison with the alkaloids quebrachamine,[15] cleavamine methiodide,[16] and capuronine,[17] which contain the same skeletal structure as **8b.** The structure of **8b** is most similar to that of quebrachamine, but differs in that the C(7)···C(8) bond is equatorial in **8b** while the corresponding bond in quebrachamine is axial. A table giving torsion angles in the piperidine and lactam rings for **8b** and **12c** and comparable angles in quebrachamine, cleavamine methiodide, and capuronine is included in the supplementary material.

Crystal Structure of 12c. The alternative mode of cyclization established for compound **12c** leads to a more highly strained macrocycle than in **8b.** Both C(7)–C(8) and C(8)–C(9) are significantly longer than in **8b,** and the endocyclic bond angles at N(3), C(2), C(7), and C(8) are larger than in **8b.** The strain is evidenced also by the displacement from planarity at C(12), which is 0.17 Å from the plane of the attached atoms. Atom C(9) is displaced by 0.6 Å from the plane of the indole ring to which it is attached. Significant deviations are also noted in the ring itself, particularly at C(19) which is 0.08 Å out of the least-squares plane. The mean deviation from planarity in the two rings is ±0.46 Å. Figure 3 provides a stereoscopic view, and a summary of bond lengths and angles is given in Figure 4.

The four atoms of the amide group centered on C(2) are planar to within 0.003 Å, whereas the amide nitrogen, N(3), is slightly pyramidal, being 0.10 Å above the plane of the attached atoms. The dioxolane ring in **12c** has an envelope conformation ($\bar{\Delta}$ = −24.8°).

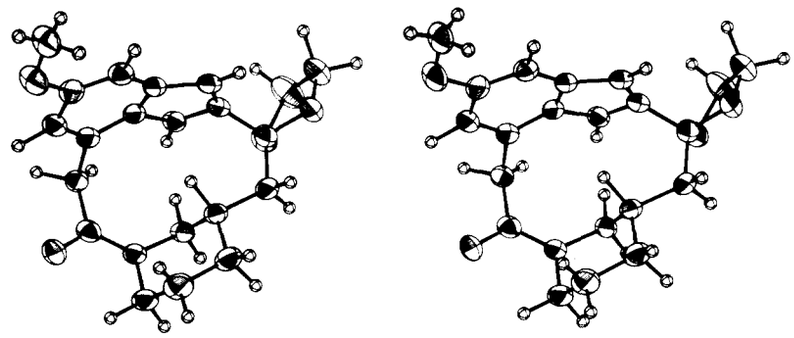


Figure 3.

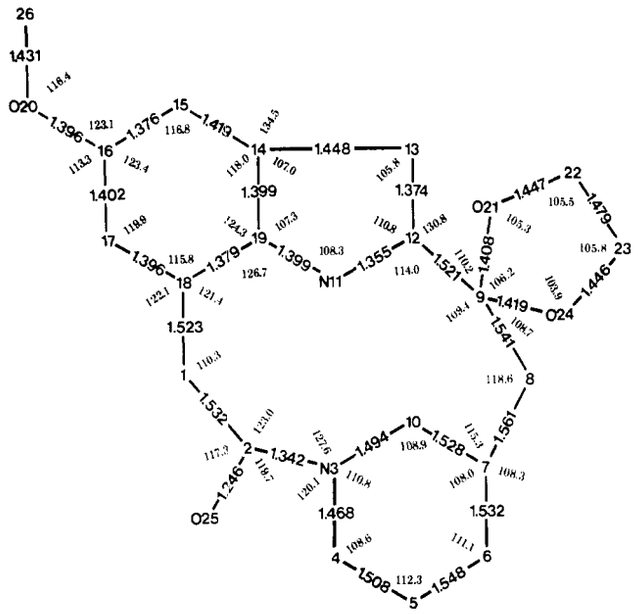
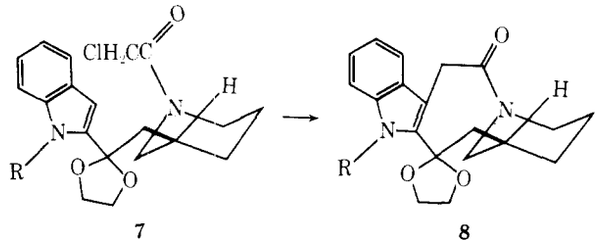


Figure 4.

There are close transannular contacts at N(11), which is only 2.91 Å from C(7) and 2.95 Å from C(10). There is a tight triangle of H···H contacts involving protons attached to C(1), C(10), and N(11).[18]

General Discussion

A comparison of the stereochemistry of the photocyclization of compounds **7a–c** with the series of four 2[(3-piperidyl)-methyl]indole derivatives examined in the earlier work[3] clarifies the relationship between ground state conformation and the stereochemistry of the photocyclization products. Three of the four 2-[(3-piperidyl)methyl]indoles gave the relatively less strained atropisomer as the major photocyclization product. In contrast, there is a consistent ratio of about 10:1 in favor of the more strained photocyclization product in each of the three 2-[(3-piperidyl)ethyl]indoles examined in the present work. We interpret the preference for formation of the less stable 8 series of products as evidence that the ground state conformation of the starting materials controls the stereochemistry of the photoproducts. Atropisomer 8



7 8

corresponds to the preferred conformation of the starting material **7**. Evidently, this conformational control of product stereochemistry is less effective in the earlier series because of the greater strain of the unstable atropisomer. The relative magnitude of the strain is considerably reduced by the incorporation of the additional methylene unit in the present series of compounds. That the strained system is formed at all in the 2-[(3-piperidyl)methyl]indole series nevertheless must reflect the fact that the biradical cation which is the key intermediate[19] is initially formed predominantly in a conformation which would lead to formation of the strained atropisomer.

In a synthetic context, this work further demonstrates[3,4] that chloroacetamide photocyclization can afford directly indoles with medium-sized C-rings in moderate yields. The reaction would appear to be competitive with polyphosphoric acid cyclization[20] for accomplishing this synthetic goal.

Experimental Section

2-Indolyl (3-Pyridyl)methyl Ketone (3a). A solution of diisopropylamine (21.4 g, 212 mmol) in 100 mL of THF was cooled to −78 °C. *n*-Butyllithium (87.5 mL of a 2.42 M hexane solution) was syringed into the solution slowly. The resulting solution of lithium diisopropylamide was allowed to stir for 0.5 h. A solution of 3-methylpyridine (19.7 g, 212 mmol) in 100 mL of THF was added, resulting in a red solution which formed a bright yellow suspension after warming to 0 °C during an additional 1.0 h. A solution of ethyl indole-2-carboxylate (10.0 g, 53 mmol) in 250 mL of THF was added dropwise over a period of 1 h, resulting in a very dark (purple) color. The solution was warmed to 25 °C and stirred for an additional 12 h. The mixture was hydrolyzed with 200 mL of saturated NH_4Cl solution, resulting in a yellow solution. The aqueous phase was separated and extracted with $CHCl_3$ (4 × 50 mL), and the $CHCl_3$ extracts were combined with the original ether phase. The combined extracts were dried (Na_2SO_4) and evaporated, leaving a yellow precipitate suspended in an oil. Trituration with ethanol left pure **3a** (7.7 g). Rapid elution through silica gel of the mother liquors with benzene–10% ethanol and crystallization from ethanol–ether gave an additional 650 mg of **3a**. The total yield of **3a**, mp 174–175 °C, was 8.35 g (67%, 35.4 mmol).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.13. Found: C, 76.39; H, 5.15.

1-Methylindol-2-yl (3-Pyridyl)methyl Ketone (3b). A solution of lithium diisopropylamide (22.2 mmol) in THF (150 mL) was prepared and allowed to react with 3-methylpyridine (1.95 g, 21 mmol) as described for **3a**. A solution of ethyl 1-methylindole-2-carboxylate (2.0 g, 10.6 mmol) in THF (20 mL) was then added dropwise at 0 °C, giving a deeply colored solution. After stirring for 0.5 h, the reaction mixture was hydrolyzed and worked up as for **3a**. The product was purified by elution through a short silica column with 1:1 ether–chloroform and crystallized from ether to give **3b** (1.92 g, 73%), mp 67–68 °C, after recrystallization from ether.

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.80; H, 5.60; N, 11.20. Found: C, 76.73; H, 5.65; N, 11.16.

5-Methoxyindol-2-yl (3-Pyridyl)methyl Ketone (3c). Lithium diisopropylamide (120 mmol) was prepared in THF (30 mL) at −78 °C and allowed to react with 3-methylpyridine (120 mmol) as described for **3a**. A solution of ethyl 5-methoxyindole-2-carboxylate (6.5 g, 30 mmol) in THF was added dropwise. After the addition was complete, the solution was allowed to come to room temperature and

stirred for 24 h. The reaction mixture was worked up as for **3a**, and the product crystallized from absolute ethanol. The mother liquors were chromatographed on silica gel using acetone for elution. The total yield of pure **3c**, mp 195–196 °C, was 6.25 g (23.5 mmol, 78%).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.26; N, 10.52. Found: C, 72.26; H, 5.27; N, 10.52.

The principal byproduct was the carbinol formed by addition of (3-pyridyl)methyllithium to **3c**. The carbinol was obtained in pure form as a hydrate, mp 170–171 °C, after recrystallization from ethyl acetate.

Anal. Calcd for $C_{22}H_{21}N_3O_2 \cdot H_2O$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.10; H, 6.18; N, 11.15.

Indol-2-yl (3-Piperidyl)methyl Ketone (4a). Compound **3a** (400 mg, 1.7 mmol) was dissolved in acetic acid (75 mL) and hydrogenated over PtO_2 (20 mg) at atmospheric pressure. The calculated amount of hydrogen (125 mL, 5.1 mmol) was taken up in a period of 2 h. The solution was centrifuged and filtered through Celite. The acetic acid was evaporated (vacuum pump), and the residue was treated with saturated aqueous sodium carbonate and extracted thoroughly with chloroform. The chloroform was dried and evaporated to an oil. Recrystallization from ethanol–water led to **4a** (225 mg, 55%), mp 153–154 °C, which was used without further purification.

5-Methoxyindol-2-yl (3-Piperidyl)methyl Ketone (4c). A solution of **3c** (10.7 g, 40 mmol) was hydrogenated for 6 h over PtO_2 (400 mg) in acetic acid (100 mL) at ~45 psi. The reaction mixture was worked up as for **3a**. The residual product was recrystallized from acetone–water, mp 135–136 °C (8.7 g, 32 mmol, 80%).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.59; H, 7.35; N, 10.29. Found: C, 70.47; H, 7.37; N, 10.28.

Indol-2-yl 1-(Chloroacetyl)piperid-3-yl Ketone (5a). Compound **4a** (3.75 g, 15.5 mmol) was added to $CHCl_3$ (250 mL) along with solid potassium carbonate (5 g). Addition of chloroacetyl chloride (3 mL) caused the solution to warm slightly. The solution was stirred for 0.5 h, and then water (8 mL) and additional chloroacetyl chloride (2 mL) were added. After stirring for an additional 15 min, saturated aqueous $NaHCO_3$ (100 mL) solution was added and the chloroform layer was collected. The aqueous phase was extracted (4 × 50 mL) with $CHCl_3$, and the combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to an oil. Crystallization from ethanol–ether yielded **5a** (3.25 g). The mother liquors were chromatographed on silica gel and yielded an additional 1.15 g of **5a** to give a total yield of 90%, mp 134–135 °C.

Anal. Calcd for $C_{17}H_{19}N_2O_2Cl$: C, 64.05; H, 6.01; N, 8.78. Found: C, 63.97; H, 6.08; N, 8.77.

5-Methoxyindol-2-yl [1-(Chloroacetyl)piperid-3-yl]methyl Ketone (5c). Reaction of **4c** (8.0 g, 29 mmol) and chloroacetyl chloride (20 mL) was carried out in $CHCl_3$ in the presence of solid potassium carbonate (15 g), similarly to the preparation of **5a**. The product was obtained in 94% yield, mp 140 °C, after recrystallization from ethanol.

Anal. Calcd for $C_{18}H_{21}N_2O_3Cl$: C, 61.98; H, 6.02; N, 8.03. Found: C, 61.82; H, 6.07; N, 7.96.

2-(Indol-2-yl)-2-([1-(chloroacetyl)piperid-3-yl]methyl)-1,3-dioxolane (7a). Compound **5a** (4.8 g, 15.1 mmol) was dissolved in benzene (250 mL), and freshly distilled ethylene glycol (15 mL) and *p*-toluenesulfonic acid (300 mg) were added. As reflux began, the solution turned a bright red. The solution was refluxed a total of 28 h in a flask equipped with a Dean-Stark apparatus. The solution was cooled and quenched with 1 N NaOH solution (100 mL). The benzene layer was collected and the aqueous phase extracted with $CHCl_3$ (4 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated, leaving a red oil. The oil was taken up in 10 mL of ethanol, and 1 mL of ether was added. **7a** precipitated (4.0 g) on standing overnight. Chromatography of the mother liquors yielded another 400 mg of **7a**, mp 151.5–153 °C. The total yield was 4.4 g, 81%.

Anal. Calcd for $C_{19}H_{23}N_2O_3Cl$: C, 62.91; H, 6.35. Found: C, 62.72; H, 6.39.

2-(1-Methylindol-2-yl)-2-([1-(chloroacetyl)piperid-3-yl]methyl)-1,3-dioxolane (7b). The intermediates **4b** and **5b** were not isolated in crystalline form. A solution of (10.0 g, 40.0 mmol) of **3b** in 250 mL of acetic acid was hydrogenated over PtO_2 (400 mg). After 24 h and uptake of ~50% of the theoretical amount of hydrogen, uptake ceased and additional (100 mg) of PtO_2 was added. Hydrogenation was complete after an additional 24 h. The solution was centrifuged and filtered through Celite. The acetic acid was evaporated at ~1 mm on a rotary evaporator, and the residue was treated with aqueous sodium carbonate and extracted thoroughly with $CHCl_3$. To the extract (~300 mL) was added solid potassium carbonate (25 g) and then chloroacetyl chloride (8 mL). The solution was stirred for 20 min (the reaction mixture warmed somewhat), and then water (10 mL) and additional chloroacetyl chloride (3 mL) were added. After 10 min, water (100 mL) was added and the layers were separated and worked up as for **5a** to give an oil (16.0 g) showing a single spot on TLC. This oil was dissolved in benzene (500 mL), and ethylene glycol (20 mL) and *p*-toluenesulfonic acid (900 mg) were added. The solution was refluxed for 48 h and worked up as for **7a** to give a glass showing a single dominant spot on TLC. This material was purified by elution through silica gel using 1:1 ether–benzene, giving 11.7 g (80% based on **3b**) of a glass which was pure by TLC. This material was used for photolysis without further purification.

2-(5-Methoxyindol-2-yl)-2-([1-(chloroacetyl)piperid-3-yl]-methyl)-1,3-dioxolane (7c). The ketalization was carried out on 9.0 g of **5c** as for **7a**. The crude product was purified by rapid elution through a silica gel column using 3:1 benzene–ether for elution. Crystallization from ethanol–ether–hexane gave **7c** (3.5 g, 35%), mp 131–132 °C, after recrystallization. The compound was somewhat difficult to crystallize efficiently and darkened to a red color on storage in the laboratory. An additional 20% yield of material slightly contaminated by **5c** was obtained by evaporation of the mother liquors.

Anal. Calcd for $C_{20}H_{25}N_2O_4Cl$: C, 61.15; H, 6.37; N, 7.13. Found: C, 60.98; H, 6.44; N, 7.09.

2-(1-Methylindol-2-yl)-2-[(3-pyridyl)methyl]-1,3-dioxolane (6b). A solution of **3b** (2.72 g, 10.9 mmol), *p*-toluenesulfonic acid (2.25 g, 13.1 mmol), ethylene glycol (13 mL), and benzene (600 mL) was refluxed with occasional monitoring of reaction progress by TLC. After 4.5 h, the solution was cooled, treated with aqueous sodium hydroxide, and extracted with ether. The extract was dried and evaporated, and the residue was chromatographed on silica gel to give **6b** (1.35 g, 4.6 mmol, 42%), mp 84–85 °C, after recrystallization from ether–hexane.

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.47; H, 6.12; N, 9.52. Found: C, 73.36; H, 6.14; N, 9.45.

Photolysis of 7a. 7a (3.6 g, 1.0 mmol) was dissolved in methanol and diluted with aqueous methanol to give 4.5 L of solution in a ratio of 60:40 methanol–water. Potassium carbonate (8 g) was added, and the solution was purged with N_2 for 0.5 h. The reaction mixture was photolyzed for 2 h. TLC indicated that all of the starting material had reacted. The solution was evaporated to about one-third its original volume (vacuum pump) and extracted thoroughly with $CHCl_3$. The extracts were dried (Na_2SO_4) and evaporated to an oil. Crystallization from $CHCl_3$ gave a precipitate slightly contaminated with polymeric material. The precipitate was redissolved in 2 mL of hot $CHCl_3$ and filtered to remove an insoluble polymer. Hot hexane (4 mL) was added, and pure **8a** was collected after cooling (1.14 g). The mother liquors were collected and chromatographed (30 g of SiO_2, 1:1:1:1 benzene–ether–hexane–$CHCl_3$) to give, after recrystallization from $CHCl_3$–hexane, one fraction of pure **8a** (0.34 g), mp 241.5–242.5 °C, and a second fraction containing a mixture of **8a** and the stable stereoisomer **9a** (0.29 g). The total yield of the isomeric photocyclization products was 54%. An analytical sample of **8a** was prepared by recrystallization from $CHCl_3$–hexane.

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.91; H, 6.79; N, 8.58. Found: C, 69.79; H, 6.81; N, 8.54.

Thermal Conversion of 8a to 9a. Compound **8a** (250 mg, 0.77 mmol) was added to 50 mL of xylene and refluxed for 24 h. A white solid precipitated on cooling. The crystals were collected by filtration and washed thoroughly with 1:1 hexane–ether and then ether. The combined xylene filtrate and ether washings were evaporated to several milliliters in volume. The resulting white crystalline residue was collected by filtration and washed with 1:1 hexane–ether. The combined crystalline product (250 mg, 100%) was pure **9a** by TLC and IR. Recrystallization of **9a** from $CHCl_3$–hexane gave an analytical sample, mp 224 °C.

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.75; H, 6.83; N, 8.53.

Hydrolysis of 8a to 10a. A solution of **8a** (66 mg) in 15 mL of refluxing methanol was treated with 10 mL of 1% hydrochloric acid and refluxed for 4 h. The solution was concentrated and extracted thoroughly with $CHCl_3$ containing about 5% methanol to dissolve the rather insoluble product. Evaporation of the dried extract gave **10a** (40 mg), which was recrystallized from ethanol–ether: mp 231–233 °C; λ_{max} 286 nm and 293 (ϵ 5.3 × 10^3) in ethanol.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.22; H, 6.46; N, 9.65.

Hydrolysis of 9a to 11a. Compound **9a** (250 mg) was added to 25 mL of a 3:2 methanol–water solution, and 0.5 mL of concentrated HCl was added. The solution was refluxed for 1 h, cooled, and evaporated to half of its original volume. The resulting suspension was diluted with 50 mL of water and extracted thoroughly with $CHCl_3$. The ex-

tract was washed with aqueous sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to a yellow oil. Crystallization from chloroform (1 mL)–hot hexane (3 mL) gave **11a** (148 mg). An analytical sample was prepared by recrystallization from chloroform–hexane: mp 216 °C; λ_{max} 242 nm (ϵ 1.1 × 10^4) and 316 (1.9 × 10^4) in ethanol.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.27; H, 6.44; N, 9.91.

Photolysis of 7b. Compound **7b** (6.1 g) was dissolved in methanol and diluted with aqueous methanol to give a total of 4.5 L of solution in a ratio of 60:40 methanol–water. Solid sodium carbonate (20 g) was added, and the solution was photolyzed for a total of 4.5 h, with the probe being removed and cleaned after 1 h. The reaction mixture was reduced to about one-third its original volume by evaporation at reduced pressure (vacuum pump), and the resulting suspension was extracted thoroughly with $CHCl_3$. The extract was dried and evaporated. The residue was dissolved in ethanol–ether and refrigerated overnight. A small amount (0.065 g) of **8b** precipitated. The major portion of product was chromatographed on silica gel using 15% ether in benzene for elution. Compound **8b** was eluted first (1.40 g), followed by a mixture of **8b** and **9b** (0.160 g) and finally pure **9b** (0.070 g). The total yield of the isomeric cyclization products was 31%. Recrystallization of **8b** from ether gave an analytical sample, mp 194–197 °C.

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.59; H, 7.06; N, 8.24. Found: C, 70.37; H, 7.13; N, 8.16.

Recrystallization of **9b** from ether gave an analytical sample, mp 204–206 °C.

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.59; H, 7.06; N, 8.24. Found: C, 70.54; H, 7.09; N, 8.19.

Thermal Conversion of 8b to 9b. A mixture of **8b** (1.27 g) and 100 mL of freshly distilled xylene was refluxed for 20 h, and most of the xylene was removed at reduced pressure. A solution of 1:1 ether–hexane was added to the crystalline residue. Filtration gave 1.13 g (89%) of **9b**, pure by TLC and IR.

Hydrolysis of 8b to 10b. A solution of **8b** (267 mg) in 3:2 methanol–water (25 mL) containing 0.8 mL of concentrated HCl was refluxed for 4 h. The solution was concentrated, neutralized, and extracted with $CHCl_3$. After evaporation of the extract, the product (62% yield) was purified by elution from silica gel with ether and recrystallized from ether: mp 174–176 °C; λ_{max} 283 nm (ϵ 5.5 × 10^3) in ethanol.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.75; N, 9.46. Found: C, 72.72; H, 6.84; N, 9.34.

Hydrolysis of 9b to 11b. A similar procedure gave a 98% yield of **11b**: mp 208–210 °C; λ_{max} 242 nm (ϵ 9.9 × 10^3) and 311 (1.1 × 10^4) in ethanol.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.75; N, 9.46. Found: C, 72.97; H, 6.78; N, 9.40.

Thermal Conversion of 10b to 11b. Quantitative conversion, as judged by TLC and identity of IR spectral data, occurred upon reflux in xylene for 10 h.

Photolysis of 7c. The chloroacetamide **7c** (3.14 g) was dissolved in methanol, and the solution was diluted to give 4.5 L of a 60:40 methanol–water solution. Sodium carbonate (20 g) was dissolved in the solution, and it was photolyzed for 2.5 h in a 5-L vessel. The solvent was reduced to a volume of ~2 L at reduced pressure and extracted thoroughly with $CHCl_3$. The extract was dried and evaporated and the residue immediately dissolved in ethanol (~5 mL). Crystallization of **8c** occurred rapidly (1.22 g). The mother liquors were evaporated, redissolved in chloroform, and chromatographed on silica gel using 3:1:1 benzene–chloroform–ether for elution. Additional **8c** (0.196 g) was eluted, followed by **9c** (0.130 g). The total yield of isomeric photoproducts was 55%. A slightly more polar fraction gave an oil from which **12c** crystallized slowly (~20 mg). An analytical sample of **8c** was prepared by recrystallization from acetone, mp 233–235 °C.

Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.41; H, 6.74; N, 7.86. Found: C, 67.35; H, 6.77; N, 7.82.

An analytical sample of **9c** was prepared by recrystallization from ethanol, mp 243–244 °C.

Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.41; H, 6.74; N, 7.86. Found: C, 67.57; H, 6.81; N, 7.74.

Thermal Conversion of 8c to 9c. Quantitative conversion of **8c** to **9c** occurred during reflux in xylene for 15 h. Evaporation of the xylene and crystallization of the residue from ethanol gave pure **9c**.

Hydrolysis of 8c to 10c. A refluxing solution of **8c** (100 mg) in methanol (15 mL) was treated with 20 mL of 1% HCl and refluxed overnight. The solution was concentrated, diluted with water, and extracted with $CHCl_3$. The solvent was dried and evaporated, and the residue crystallized from ethanol–ether: mp 213–218 °C; λ_{max} 277 nm (ϵ 4.8 × 10^3) and 307 (5.5 × 10^3) in ethanol.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.18; H, 6.49; N, 8.95.

Hydrolysis of 9c to 11c. A solution of **9c** (350 mg) in 60 mL of methanol was treated with 40 mL of 1% HCl and refluxed for 1.5 h. TLC indicated quantitative conversion to **11c**. The solution was worked up as for **10c**, and **11c** was recrystallized from ethanol–water to give yellow crystals: mp 258–260 °C; λ_{max} 324 nm (ϵ 1.6 × 10^4) in ethanol.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.96; H, 6.51; N, 8.90.

Table II. Crystallographic Data

	8b	12c
formula	$C_{20}H_{24}N_2O_3 \cdot 0.5H_2O$	$C_{20}H_{24}N_2O_4$
M_r	349.4	356.4
space group	$P2_1/c$	$P2_1/c$
a, Å	11.233 (5)	13.956 (3)
b, Å	17.874 (7)	10.379 (2)
c, Å	18.358 (12)	16.264 (5)
β, deg	103.99 (6)	130.08 (5)
volume, Å^3	3577	1803
d_c, g cm^{-3}	1.298	1.313
d_o, g cm^{-3}	1.29	1.31
Z	8	4
F (000)	1496	760
μ, cm^{-1}	7.0	7.6
λ, Å	1.5418	1.5418
R	0.063	0.063
R_w	0.094	0.061

X-ray Crystallographic Measurements. Relevant crystallographic data for the two compounds are given in Table II. Unit cell symmetry and preliminary cell dimensions were found from 25° precession photographs taken with Mo Kα radiation. Accurate cell dimensions were found by a least-squares fit to the diffractometer values of $\pm 2\theta$ for 24 strong general reflections from carefully centered crystals.

Intensity measurements were made in each case from equidimensional prisms, 0.3 and 0.35 mm on a side, using a Picker full-circle diffractometer operated under the control of an XDS Sigma 2 computer. The θ–2θ scan method was used with scan ranges of 2° in 2θ and a scan speed of 2° min^{-1}. Background intensity measurements were made at the beginning and end of each scan with crystal and counter stationary over 15-s intervals. Cu Kα radiation was used, made monochromatic by Bragg reflection from a highly oriented graphite crystal. Scintillation counting was used with pulse-height analysis. To check crystal alignment, the intensities of the symmetry related $0kl$ and $0k\bar{l}$ reflections were measured separately. These showed a mean deviation about their mean intensities of 3.5% in the case of **8b** and 3.2% for **12c**. Stability of the experimental conditions was monitored by measurement of the intensities of two symmetry related reference reflections after every 30 scans. No significant variation in intensity was noted. No absorption corrections were applied, with the variation in intensity as a function of path length not being calculated as greater than 5% for either crystal used. Lorentz and polarization factors were applied, and structure amplitudes and normalized structure amplitudes were derived.

Structure Determination and Refinement. Both structures were solved by the routine application of the program MULTAN.[21] In **8b**, the correct E map showed 49 of the atomic sites in the two crystallographically independent molecules. The remaining atom and the single water of hydration in the asymmetric unit were found from a difference electron density map. In **12c**, the 26 highest peaks in the E map corresponded to atomic sites.

Both structures were refined by block-diagonal least-squares methods (3 × 3, 6 × 6 blocks) with anisotropic thermal parameters being used for the C, N, and O atoms. Hydrogen atoms, other than those of the water molecule in **8b** which were not detectable, were located from three-dimensional electron density maps. For **8b**, contributions from these hydrogen atoms in fixed optimized positions[22] and with isotropic thermal parameters set equal to the equivalent isotropic B value for the atom of attachment were included in the least-squares calculations. For **12c**, the observed positions were not optimized, but contributions for the hydrogen atoms in fixed positions and with isotropic B values set equal to $B + 1$ for the atom of attachment were included. A conventional weighting scheme[23] was

adopted in each case, and refinement continued until no calculated shift in any parameter exceeded one-tenth of the corresponding esd.

Scattering functions for C, N, and O were taken from "International Tables for X-Ray Crystallography"[24] and for H from the compilation of Stewart, Davidson, and Simpson.[25] With the exception of MULTAN and ORTEP,[9] for which a CDC Cyber 172 computer was used, all calculations were carried out on an XDS Sigma 2 computer with programs written in this laboratory.

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Registry No.—**3a,** 67921-99-7; **3b,** 67922-00-3; **3c,** 67922-01-4; **4a,** 67922-02-5; **4c,** 67922-03-6; **5a,** 67922-04-7; **5c,** 67922-05-8; **6b,** 67922-09-2; **7a,** 67922-06-9; **7b,** 67922-07-0; **7c,** 67922-08-1; **8a,** 67922-10-3; **8b,** 67951-69-3; **8c,** 67922-11-6; **10a,** 34964-86-8; **10b,** 67951-68-2; **10c,** 67922-12-7; **12c,** 67951-67-1; lithium diisopropylamide, 4111-54-0; 3-methylpyridine, 108-99-6; ethyl indole-2-carboxylate, 3770-50-1; ethyl methylindole-2-carboxylate, 18450-24-3; ethyl 5-methoxyindole-2-carboxylate, 4792-58-9; chloroacetyl chloride, 79-04-9; ethylene glycol, 107-21-1; (3-pyridyl)methyllithium, 26954-24-5; 5-methoxy-α,α-bis[(3-pyridinyl)methyl)]-1*H*-indole-2-methanol, 67922-13-8.

Supplementary Material Available: Fractional coordinates with estimated standard deviations for C, N, and O atoms for compounds **8b** and **12c,** ansisotropic thermal parameters for molecules A and B in **8b** and for **12c,** bond distances and estimated standard deviations for **8b** and **12c,** bond angles for **8b** and **12c,** selected torsional angles for the nonaromatic rings in **8b** and **12c,** and information on least-squares mean planes (13 pages). Ordering information is given on any current masthead page.

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(11) However, if the esd's derived from the least-squares matrices are accepted, apparently significant deviations from the mean values of the bond lengths ($\Delta > 2\sigma$) in A and B are found for C(7)–C(10), C(16)–C(17), and O(21)–C(22). At least in the case of the first two of these distances, there is no reason to expect these differences to have physical significance. It seems wiser to assume that the esd's are underestimated, and by assuming their true values to be 1.5 times those quoted, none of the differences found in chemically equivalent bond lengths and angles would be significant.
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Reaction of 2-(1-Alkoxyethylideneamino)benzophenones with Amines. A Novel Synthesis of 2-(*N*-Substituted-amino)-4-phenylquinolines

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When 2-(1-alkoxyethylideneamino)benzophenones (**1**) were allowed to react with aminoacetaldehyde dialkyl acetals (**2**) in alcohol using an acid catalyst, 3-(2,2-dialkoxyethyl)-3,4-dihydro-4-hydroxy-2-methyl-4-phenylquinazoline (**3**) was obtained in 51–70% yield after silica gel column chromatography together with the minor products 2-(2,2-dialkoxyethylamino)-4-phenylquinoline (**4**) and 2-aminobenzophenone (**5**). On the contrary, the reaction of **1** with **2** in toluene or xylene afforded a 56–76% yield of **4** as the major product. Heating of a xylene solution of **3** with an acid effected the conversion of **3** to **4**. Mechanistic pathways of the above reactions are presented.

2-(*N*-Substituted-amino)-4-phenylquinolines have typically been synthesized[1–4] from the corresponding 4-phenylcarbostyrils. In the course of synthetic studies on tricyclic diazepine compounds,[5] we have investigated the reaction of 2-(1-alkoxyethylideneamino)benzophenones (**1**) with amines, which led to a novel, convenient synthesis of 2-(*N*-substituted-amino)-4-phenylquinolines. The related reaction of **1** or 5-chloro-2-(acylamino)benzophenones with hydrazine hydrate has been reported to give 3,4-dihydro-4-hydroxy-4-phenylquinazolines.[6,7]

Results and Discussion

Compounds **1** were allowed to react with aminoacetaldehyde dialkyl acetals (**2**) using *p*-toluenesulfonic acid or sulfuric acid as the catalyst, and the results summarized in Table I were obtained. When the reactions were run in etha-

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