Photocyclization of 2-(*N*-Chloroacetylpiperidylalkyl)indoles. A Novel Case of Stereoisomerism Dependent on Sterically Restrained Conformations

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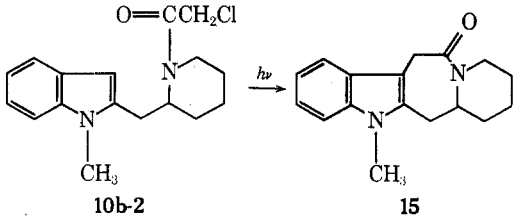
A series of 2-(*N*-chloroacetylpiperidylalkyl)indoles has been prepared. The photolysis of these compounds, in general, leads to cyclization resulting from alkylation of the indole 3 position by the chloroacetyl group when the indolylalkyl group is attached to the 2 or 3 position of the piperidine ring. A competing process observed in some reactions involves cyclization at a substituent group. This photocyclization permits fusion of seven- and eight-membered rings to the b side of the indole ring with moderate efficiency. A novel case of stereoisomerism was observed in certain of the resulting bicyclic amides.

Several years ago Yonemitsu, Cerutti, and Witkop reported a novel photocyclization of the chloroacetamide of tryptophan in which the chloroacetyl group alkylated C-4 of the indole ring.[2] Since that time photocyclization of aromatic chloroacetamides has been studied from a mechanistic point of view[3] and applied synthetically,[4] but with few exceptions[5] the subsequent studies have been focused on phenols and methoxy aromatics. We wished to develop a procedure of reasonable generality for the annelation of the b side of the indole ring with medium-sized nitrogen-containing rings. The recent demonstration that 2-lithioindoles[6] can serve as versatile precursors of pyridylalkylindoles led us to investigate the preparation and photocyclization of the *N*-chloroacetyl derivatives of the corresponding piperidines.

Scheme I shows the routes of synthesis of the amides studied in this work. In general, these reactions require no specific comment other than that they further document the synthetic utility of the 2-lithioindole intermediates. The catalytic reductions and acylations with chloroacetyl chloride or chloroacetic anhydride were straightforward in most cases. Table I gives the melting points and recrystallization solvents for new compounds prepared in the course of this work. The source of other intermediates are also indicated in footnote *a* of Table I.

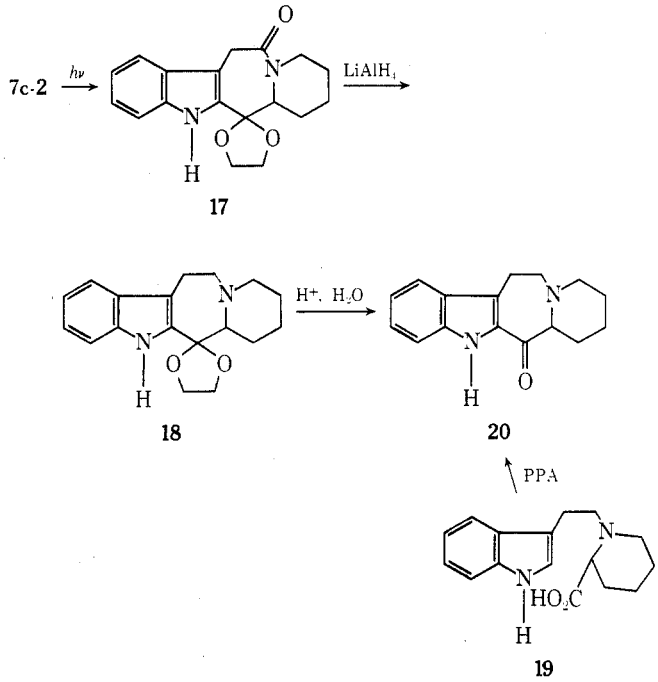
The photocyclization reactions were usually carried out in methanol. Benzene and 1-propanol were used for comparison in some cases. Benzene was not as satisfactory as methanol. Solid sodium carbonate was added in the case of the ketals, to eliminate hydrolysis. The reaction times varied markedly from compound to compound and were quite short in some cases. The identification of the individual photoproducts is discussed in the paragraphs which follow. The structures, yields, and certain physical properties of the photoproducts are given in Table II for those systems where cyclization was observed.

Photolysis of **10b-2** gave a single isolable photoproduct in 36% yield. The product was expected to be **15** and all



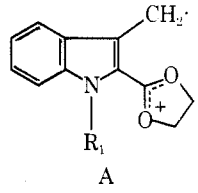
10b-2 **15**

available spectral data are in accord with this structure. The NMR spectrum shows no indole 3-H indicating the point of cyclization. The base peak in the mass spectrum is at *m/e* 157 consistent with a 2,3-disubstituted 1-methylindole. The ultraviolet spectrum is typical of an indole chromophore. Cyclization took a similar course when the ketals **7b-2** and **7c-2** were photolyzed. The structure of **17** the photoproduct from **7c-2** was proven by interrelating it with **20,** which was prepared by an alternative route involving polyphosphoric acid cyclization of **19,** which was prepared



17 **18** **20** **19**

from tryptophyl bromide and methyl piperidine-2-carboxylate.[7] The spectroscopic properties of **16** and **17** were also in accord with the assigned structures. In both cases the base peak in the mass spectrum appeared at the mass corresponding to ion A. The NMR spectra indicated that cy-

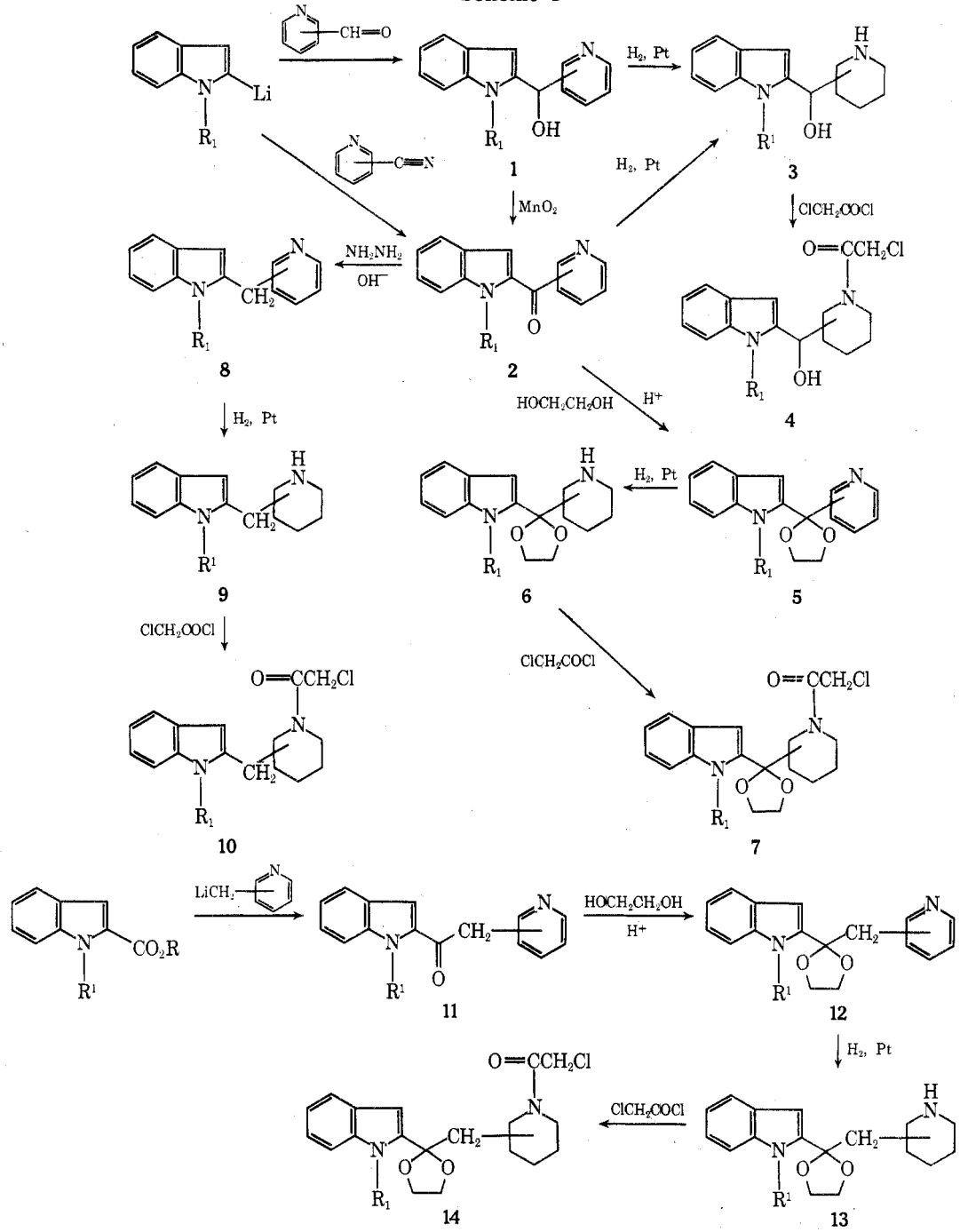


A

clization had occurred at the 3 position because of the absence of the characteristic 3-H signal. The ketones **21** and **22,** respectively, obtained by hydrolysis of **16** and **17,** were also characterized by spectral data and elemental analysis.

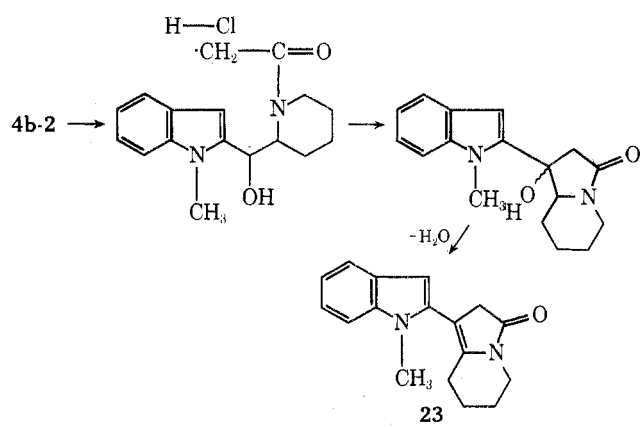
Two other compounds having the same 2-indolyl-2-piperidylmethane structural framework did not cyclize to C-3 on photolysis. Both diastereomers of the alcohol **4b-2**

Scheme I[a]



[a] Not all of the possible permutations were investigated. The compound numbers in Table I indicate which compounds have been synthesized. The designations **a**, **b**, or **c** specify the indole 1 substituent and **-2**, **-3**, or **-4** the point of attachment to the piperidine ring: **a**, $R_1 = PhSO_2$; **b**, $R_1 = CH_3$; **c**, $R_1 = H$.

formed a mixture of two unstable photoproducts presumed to be diastereomeric hydroxypyrrolidones. Both unstable photoproducts dehydrated to give **23**. The NMR spectrum indicates that a 3-H proton remains on the indole ring and also reveals a two-proton singlet at δ 3.40 which can be assigned to the methylene group of the dihydropyrrolone ring. The ultraviolet spectrum also shows that the chromophore is more extended than that of a simple indole ring. An alternative structure which was considered would be the dehydration product of the alcohol formed by cyclization at C-3 of the indole ring. To rule out this structure compound **21** was reduced with $NaBH_4$. The reduction product was stable in refluxing methanol in contrast to the facile dehydration of the precursors of **23**. Also in agreement with the assignment of structure **23** is the fact that

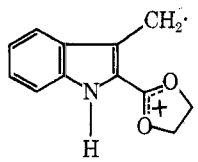


the methylene group was readily exchanged in aqueous sodium bicarbonate, as would be expected for a dihydropyrrolone. This type of cyclization, involving a substituent group in preference to the aromatic ring, has been formulated in terms of an intramolecular abstraction recombination mechanism.[3a,c,4i] The carbinyl hydrogen in **4b-2** may be particularly prone to abstraction, since the resulting radical is stabilized both by the indole ring and the hydroxyl group.

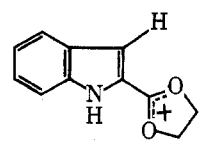
The *N*-benzenesulfonyl compound **7a-2** was apparently converted to the 3-benzenesulfonyl derivative **24** on photolysis with no involvement of the chloroacetyl group. The product is isomeric with starting material but lacks an indole 3-H in the NMR spectrum. Photoisomerization of 1-tosylindoles to 3-tosylindoles has been recorded.[8]

When the connecting chain between the piperidine and indole ring was lengthened to two atoms, the cyclization still proceeded but in somewhat decreased yield. Photolysis of **14b-2** gave a ~20% yield of **25**. The structure of this compound is assigned on the basis of analogy with the preceding compounds and consistent spectral properties including the absence of an indole 3-H signal. The corresponding ketone was also obtained by hydrolysis. Its NMR spectrum is also consistent with the assigned structure.

The compounds which were investigated in the 3-piperidyl series were **7b-3, 7c-3, 10b-3,** and **10c-3.** Structural investigation of the photoproducts from **7c-3** set the pattern for the other systems and will be discussed first. Two isomeric ketals were obtained on photolysis of **7c-3** and were separated by chromatography. The major product **33** (35%, mp 188–189°) was less polar than the minor product **34** (9%, mp 194–196°) on silica gel. Both appeared to be cyclized products since neither shows an indole 3-H signal, both have normal indole ultraviolet absorbance spectra, and both show peaks corresponding in mass to ions B and C as major peaks in their mass spectra. Indeed, the mass



B



C

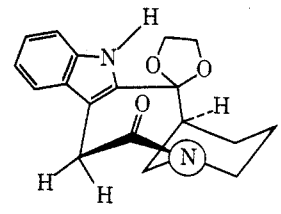
spectra of the two compounds are virtually identical. Acidic hydrolysis gave two ketones, **35** from **33** and **36** from **34**. Ketone **35** was converted to **36** by treatment with sodium ethoxide in ethanol.

The 300-MHz ^{1}H NMR spectrum of the stable isomer **36** is completely interpretable in terms of the assigned structure. The nonaromatic portion of the spectrum is shown in Figure 1. There are sufficient overlaps even in the 300-MHz spectrum of the unstable isomer **35** that it cannot be completely analyzed. However the fact that **35** is converted to **36** by mildly alkaline conditions and the near identity of the mass spectra of the two compounds argue against the possibility that the aliphatic portions of the structures of **35** and **36** might be different. The NMR and ultraviolet spectra leave no doubt that both compounds are 2,3-disubstituted indoles. These facts suggest that **33** and **34** (as well as **35** and **36**) are stereoisomers. The only stereoisomerism possible is in the formation of the bicyclic ring system. There are two ways in which the five-membered bridge of the bicyclic ring can be closed. If the ring closure is made with the side chain at C-3 of the piperidine ring in an axial position, the relatively unstrained ring system **34** results. Minor strain in this system results from partial double bond character in the amide at the bridgehead position. If, on the other hand, the ring is closed with the C-3 side chain in an equatorial position, a highly strained bicyclic system (**33**) results. The two rings can be interconverted by single bond rotations which pass the C-2 methylene of the piperidine ring through the bicyclic ring but this appears from models to be strongly prohibited by nonbonding interactions between the methylene hydrogens and the C-2–C-3 carbons of the indole ring.

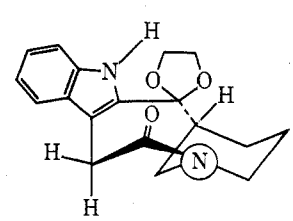
Table I
Synthetic Intermediates[a]

Compd	Mp, °C	Recrystn solvent
1b-4	167–168	Acetone–ether
2b-2	78–79	Ether–heptane
2b-3	87–88	Acetone–ether
4a-4	178–179	Acetone
4b-2[b]	142–143,	Ether
	156–157	Ether
5b-2	113–114	Ether
5b-3	105–106	Ether
5c-2	180–181	Dichloromethane–hexane
5c-3	127–129	Dichloromethane–hexane
7a-2	197–198	Acetone–ether
7b-2	148–150	Acetone–ether
7b-3	142–143	Acetone–ether
7b-4	106–108	Ether
7c-2	162–163	Acetone–ether
7c-3[c]		
8b-2	68–69	Heptane
8b-3	58–59	Heptane–ether
8b-4	64–65	Hexane
9c-3	172–173	Methanol–benzene
10b-2	76–78	Ether
10b-3[c]		
10b-4[c]		
10c-3	138–140	Ethyl acetate–ether
11b-2	68–70	Hexane–ether
11c-4	168–169	Acetone–ether
12c-4	208–207	Acetone–ether
14b-2	143–144	Chloroform–ether
14c-4	139–141	Chloroform–ether

[a] The following intermediates have been previously described in ref 6: **1a-2, 2a-2, 2a-3, 2a-4, 2c-2, 2c-3.** Alternative syntheses for some of the intermediates have been reported: **2c-2,** R. J. Sundberg, H. F. Russell, W. V. Ligon, Jr., and L.-S. Lin, *J. Org. Chem.*, **37,** 719 (1972); **2b-4, 2c-4,** A. Jackson, N. D. V. Wilson, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc. C,* 2738 (1969); **8c-2, 8c-3, 8c-4,** M. Hooper and W. N. Pitkethly, *J. Chem. Soc., Perkin Trans. 1,* 1607 (1972); **9c-4,** J. Eenkhoorn, S. O. de Silva, and V. Snieckus, *Can. J. Chem.*, **51,** 792 (1973). [b] Two diastereomers were separated. [c] Not obtained in crystalline form.



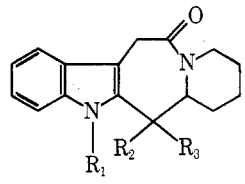
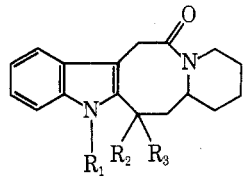
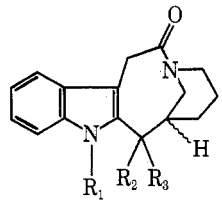
34



33

The nature of the stereoisomerism is related to that which is possible in bicyclic ring systems in which one of the bridges is sufficiently large to permit ring closure involving branches having a trans relationship relative to the

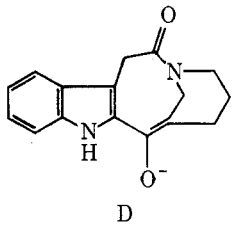
Table II
Cyclic Photoproducts and Derivatives

Compd	R_1	R_2	R_3	% yield[a]	Mp, °C	Recrystn solvent
						
15	CH_3	H	H	36	253–254	Acetone–ether
16	CH_3	$-OCH_2CH_2O-$		41	259–260	Chloroform–ether
17	H	$-OCH_2CH_2O-$		58	248–249	Ethyl acetate–ether
21	CH_3	=O			225–226	Ethanol–ether
22	H	=O			267–269	Chloroform–ether
						
25	CH_3	$-OCH_2CH_2O-$		20	178–179	Chloroform–ether
26	CH_3	=O			146–147	Ether
						
27[b]	CH_3	$-OCH_2CH_2O-$		5	226–227	Ether
28[b]	CH_3	$-OCH_2CH_2O-$		23	162–164	Ether
29[c]				5	185–186	Chloroform–ether
30	CH_3	=O			220–221	Chloroform–ether
31[c]					205–207	Methanol–water
32[c]					200–202	Ether
33[b]	H	$-OCH_2CH_2O-$		35	188–189[d]	Acetone–ether
34[b]	H	$-OCH_2CH_2O-$		9	194–196	Acetone–ether
35[b]	H	=O			286–287	Methanol–water
36[b]	H	=O			291–292	Ethanol–ether
37[b]	CH_3	H	H	15	227–228	Acetone–ether
38[b]	CH_3	H	H	7	192–193	Ether
39[b]	H	H	H	21	268–270	Chloroform–ether
40[b]	H	H	H	9	303	Chloroform–ether

[a] Yields are recorded only for photocyclization reactions. [b] See text for stereochemical assignment. [c] See text for structure. [d] Melts with desolvation; with very slow heating there is some resolidification followed by remelting at 240°.

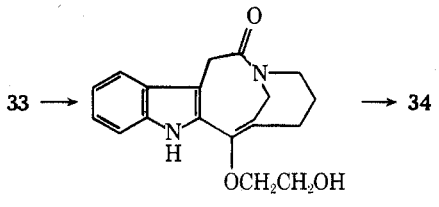
other component ring.[9] However, because of the planar character of the amide nitrogen the existence of stereoisomers also depends upon the conformational locking achieved by steric prohibition of chair–chair interconversion in the piperidine ring.

The conversion of **35** to **36** in basic solution can occur through the common enolate D. When this equilibration was carried out in the presence of D_2O in DMSO-d_6, the product was **36** consisting of a mixture of the d_3 and d_2 isotopic species. The location of the additional deuterium is in the methylene group adjacent to the amide carbonyl, so enolization of the amide group is apparently competitive with enolization at the bridgehead position adjacent to the ketone carbonyl. This probably reflects decreased amide character as a result of the ring strain. The carbonyl peak in **33** is at 1645 cm^{-1} as compared to 1635 cm^{-1} for **34**.



D

Thermal conversion of the ketal **33** to **34** occurs slowly at 170°. A series of experiments in which solutions of **33** in bis(2-ethoxyethyl) ether were sealed under nitrogen and



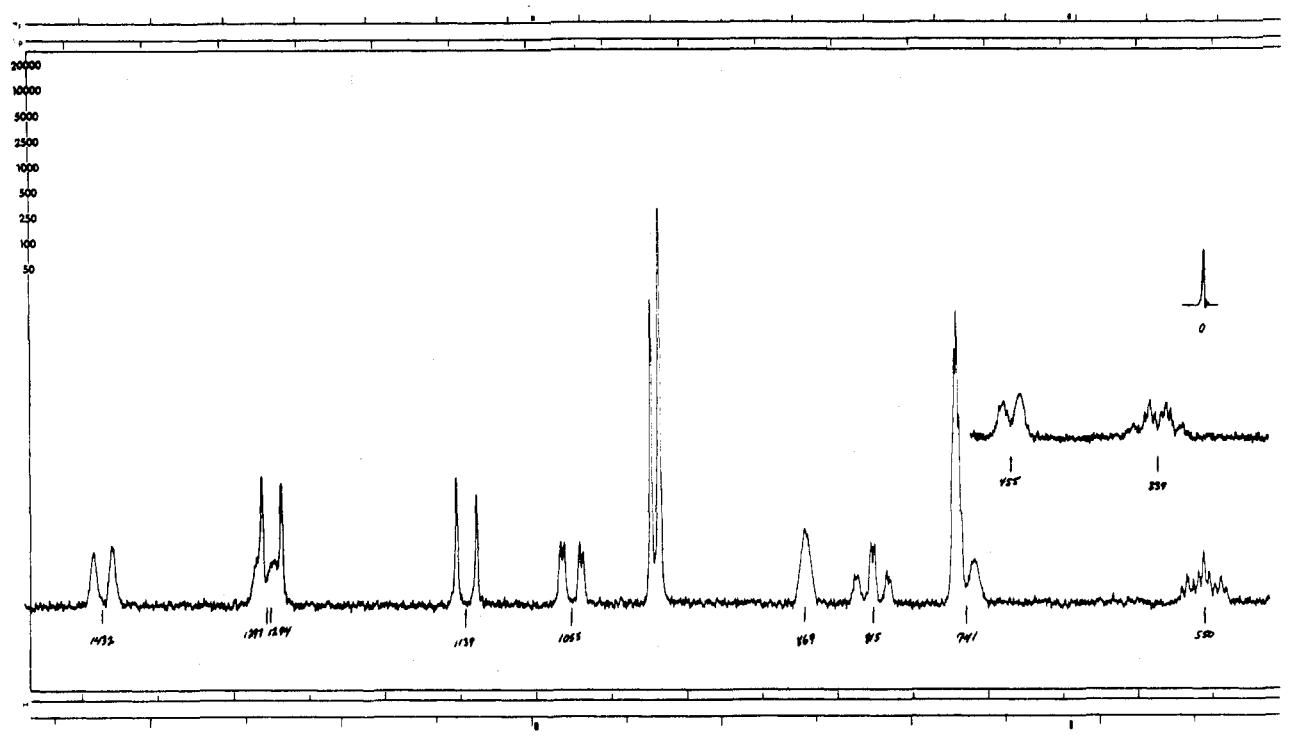


Figure 1. Proton NMR (in DMSO-d_6) of compound **36**. Chemical shifts are given in hertz from Me_4Si. Assignments are given with reference to the numbering given in Table III. 337, q of t, J = 12, 3 Hz (C-5 ax); 455, broad d, J = 12 Hz (C-5 eq); 550, t of t, J = 13, 4 Hz (C-4 ax); 741, broad d partially obscured by DMSO-d_5 (C-4 eq); 815, t of d, J = 13, 3 Hz (C-6 ax); 869, broad s (C-3); 1055, J = 15, 3 Hz (C-2 ax); 1139, 1294, AB doublets, J = 16 Hz (C-8 methylene); 1297, broad d partially obscured by AB doublet (C-6 eq); 1432, broad d, J = 13 Hz (C-2 eq).

maintained at 170° gave variable half-lives for the conversion, ranging from ~2.5 to ~8 hr. The reaction is apparently quite sensitive to adventitious catalysts. It is not clear that the thermal process which accomplishes the isomerization is purely conformational. It is quite possible that a reversible elimination might be involved.

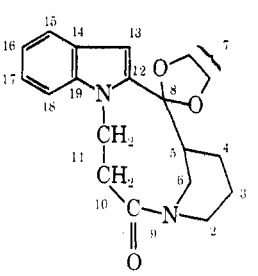
The ^{13}C chemical shifts of compounds **35** and **36** are given in Table III. The multiplicities in off-resonance decoupled spectra are given in parentheses. The number of peaks of each multiplicity and the general chemical shifts are in accord with the assigned structures. The most notable shifts in the spectra between the two isomers are at the two carbonyl carbons (C-7 and C-9) at C-2, C-3, and C-8. The shifts are downfield in the strained isomer **35** at the aliphatic carbons. Since steric compression normally results in an upfield shift, it seems unlikely that the observed shifts are due to this cause, although models indicate that the C-8 methylene group can interact with the hydrogens on both C-2 and C-3. The downfield shift is perhaps related to the ring strain. The relative chemical shifts of the bridgehead carbons of bicyclo[2.2.2]octane, 23.9 ppm,[10a] and bicyclo[2.2.1]heptane, 36.8 ppm,[10b] suggest that ring strain may cause a downfield shift at sp^3 carbon atoms. The large shifts in the carbonyl groups may reflect differing degrees of conjugation or coplanarity with nitrogen and the indole ring as the result of the ring strain. The assignment of C-8 was made on the basis of gated decoupling[11] spectra of **35** and **36** which showed one of the upfield triplets (C-8) to have much less long-range coupling than the others.

At least one of the indole ring carbons shows a substantial downfield shift in **35** and **36** relative to **33** and other indoles[12] lacking 2-carbonyl groups. Resonance considerations suggest that C-15 and C-13 would be most strongly affected. In the absence of model compounds we have not made assignments to the three closely spaced aromatic carbons.

The ^{13}C NMR spectrum of the strained ketal **33** was recorded. The data are given in Table III. This spectrum exhibits no chemical shifts which are grossly discordant with previously reported spectra of indole derivatives,[12] although, of course, no close model for the strained ring system in **33** exists. The multiplicity of the peaks in the off-resonance decoupled spectrum is compatible with the assigned structure.

Three products, **27** (5%), **28** (23%), and **29** (5%), were obtained from the *N*-methyl compound **7b-3** when photolyzed in methanol. Two of these, **27** and **28**, appeared to be the stereoisomeric *N*-methyl analogs of **33** and **34** on the basis of the characteristic disappearance of the indole 3-H proton from the NMR spectra of these cyclization products. Methylation of the anion of **34** in dimethyl sulfoxide with methyl iodide led to **28**, confirming the structural relationship. The ketone, **30**, corresponding to **28** was obtained by acidic hydrolysis and characterized by elemental analysis and spectral data.

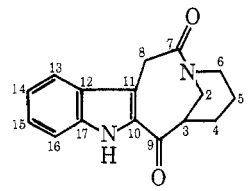
The third photoproduct, **29**, was formed in only 5% yield



29

in methanol, but the yield was around 20% when the photolysis was carried out in benzene or 1-propanol. It retained an indole 3-H proton as was evident from the ^1H NMR spectrum but the *N*-methyl signal was missing. This provided the initial basis for assigning structure **29**. The ^{13}C NMR spectrum, which is given in Table IV, is consistent

Table III
^{13}C NMR Spectra of Compounds 33, 35, and 36[a]

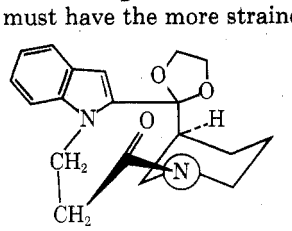


Carbon	33	35	36
2	52.8[b] (t)	54.5[b] (t)	46.3[b] (t)
3	56.0 (d)	58.6 (d)	48.0 (d)
4, 5	24.6, 26.6 (t)	23.6, 25.0 (t)	22.7, 26.7 (t)
6	45.1[b] (t)	45.3[b] (t)	42.0[b] (t)
7	177.0 (s)	177.2 (s)	169.5 (s)
8	~39.5[c]	39.0 (t)	33.1 (t)
9	107.7[d] (s)	189.8 (s)	196.3 (s)
10	134.3 (s)	132.7[g] (s)	132.5[g] (s)
11	106.2[d] (s)	116.1 (s)	114.7 (s)
12	128.3 (s)	128.2 (s)	127.7 (s)
13	118.8 (d)[e]	125.1 (d)	125.6 (d)
14	122.2 (d)[e]	120.1 (d)	120.8 (d)
15	118.4 (d)[e]	119.9 (d)	119.8 (d)
16	111.3 (d)[e]	112.5 (d)	112.2 (d)
17	137.3 (s)	135.0[g] (s)	135.5[g] (s)
	65.9, 65.3[f] (t)		

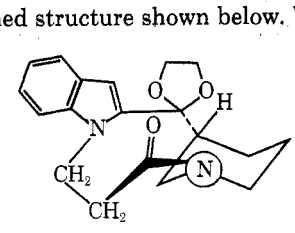
[a] Spectra were recorded in DMSO-d_6 with internal Me_4Si reference. Multiplicities were determined by off-resonance decoupling or gated decoupling.[11] [b] C-2 and C-6 assignments could possibly be interchanged. [c] Buried in DMSO-d_6. [d] C-9 and C-11 might be interchanged. [e] Assignments made in analogy with chemical shift relationships reported in ref 12. [f] Carbons of dioxolane ring. [g] Assignments of C-10 and C-17 might be reversed.

with the assigned structure. The peak at 103.3 is a doublet in the off-resonance decoupled spectrum, in agreement with the conclusion that the 3 position of the indole ring is unsubstituted. There are no quartets in the off-resonance decoupled spectrum, in agreement with the conversion of the *N*-methyl to a methylene group. Formation of **29** presumably involves a hydrogen abstraction–recombination mechanism. The reaction is similar to cyclizations involving methoxy substituents in some of the earlier studies.[3c,4i,k]

The ring system present in **29** should be capable of the same type of conformational isomerism detected in **33–34** and analogous pairs. For this reason, the stability of **31**, the ketone derived from **29**, in basic solution was examined. It was found to give an isomeric ketone **32**. The ketal evidently must have the more strained structure shown below. We



not observed



29

did not detect the less strained isomer as a photolysis product.

Both **10b-3** and **10-3** also gave two isomeric photocyclization products. For the *N*-methyl series a major product, **37** (15% yield, mp 227–228°), and minor product, **38** (7% yield, mp 192–193°), were obtained. From the unmethylated starting material **39** (21% yield, mp 268–270°) and **40** (9% yield, mp 303°) were obtained. The two major products

Table IV
Partial Assignment of ^{13}C NMR Spectrum of 29[a]

Carbon	Signal	Multiplicity
5	51.5	d
8	107.0	s
9	173.9	s
12	138.1	s
13	103.3	d
14	126.6	s
15	120.3	d
16	122.9	d
17	121.3	d
18	109.5	d
19	140.2	s

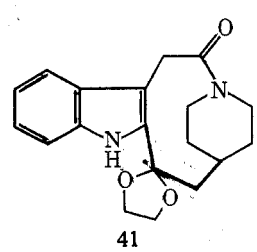
[a] Other signals, all of which are triplets in the off-resonance decoupled spectrum, are at 67.5, 63.3, 51.0, 45.7, 41.6, 40.3, and 25.2 ppm. One set of superimposed signals is required by the number of observed peaks and this is probably the two methylene groups of the dioxolane ring. Definitive assignments of these peaks is not possible. The following seem most likely: C-7, 67.5; C-2, C-6, 63.3, 51.0; C-11, 45.7; C-3, C-10, 41.6, 40.3; C-4, 25.2.

were interrelated by methylating **39** to give **37**. Compound **39** was also obtained by reducing the ketone **36** with triethylsilane in the presence of trifluoroacetic acid.[13] This not only relates the products from the **7-3** and **10-3** series of starting materials but also permits the conclusion that the major products **37** and **39** have the less strained stereochemistry of ketal **34**. It is assumed that the minor photoproducts **38** and **40** are the strained stereoisomers corresponding to ketal **33**, since all the spectroscopic data indicate that the gross structure of the minor isomer is identical with that of the major product in both cases.

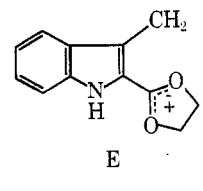
Thermal conversion of **40** to **39** was observed at 170° in bis(ethoxyethyl) ether but was exceedingly slow, being less than half complete after 60 hr.

No photocyclication products were observed in the 4-piperidylmethyl series. Attempts were made with the ketal **7b-4** and with **10b-4**. This may reflect a strong preference for an equatorial conformation for the indolyl substituent. In this conformation the indole ring and chloroacetyl substituent may be too remote for the electron transfer which is required for photocyclization.[3] It should be noted, however, that Snieckus and coworkers[5b] have achieved successful cyclization in this structural series using compound **10c-4**.

In the case of compound **14c-4**, in which an additional methylene group is interposed, some photocyclization apparently occurs. Composed **41**, in which the new ring formed is ten-membered, was isolated in trace yield. The



41



E

evidence for the assigned structure is the presence of a peak of the expected mass for the parent ion and for ion E in the mass spectrum. The amount of material was too small for complete characterization, however.

In several of the photocyclizations some formation of the acetyl derivative by dechlorination of the chloroacetyl group was observed. This has been observed before[3,4] and presumably involves a hydrogen abstraction from solvent.

The identity of these products was generally evident from the NMR spectrum. No effort was made to fully characterize this group of photoproducts.

The pattern which seems to emerge from these results is that the photocyclization is capable of forming medium-sized rings, even highly strained ones, if the indole ring and chloroacetyl substituent can achieve reasonable proximity to one another. It is interesting to note that in the case of photolysis of **7c-3** the more highly strained product which predominates is related to the more stable conformation of the starting material. No general argument for control of the product stereochemistry by reactant conformation can be developed, however, because in each of the other three 2-indolyl-3-piperidylmethane derivatives which were studied (**7b-3, 10b-3, 10c-3**), the less strained bicyclic ring system was the predominant product.

Experimental Section

2-Indolyl Pyridyl Ketones (2). The ketones were prepared from 1-methyl-2-lithioindole or 1-benzenesulfonyl-2-lithioindole by reaction with the appropriate cyanopyridine as described by Sundberg and Russell[6] or by a two-step procedure from the lithioindole and pyridinecarboxaldehyde followed by manganese dioxide oxidation. The preparations of **2a-3** and **2c-3** are illustrative of the latter procedure. A solution of 0.1 mol of 1-benzenesulfonyl-2-lithioindole in tetrahydrofuran was prepared following the procedure of Sundberg and Russell[6] and allowed to warm to room temperature. To this solution there was added slowly by syringe 10.0 ml of 3-pyridinecarboxaldehyde. The reaction mixture was stirred for 1 hr and then hydrolyzed with water. The product was obtained by extraction with methylene chloride. The residue crystallized when dissolved in a small amount of benzene, giving **1a-3** in 60% yield. This was not purified further but was dissolved in chloroform and stirred overnight with 50 g of activated manganese dioxide.[14] Clean conversion to **2a-3** occurred and the product was isolated in 94% yield. The infrared spectrum was identical with that of a previously prepared sample.[6] The hydrolytic removal of the *N*-benzenesulfonyl group to give **2c-3** has been previously described.[6]

Dioxolane Derivatives of 2-Indolyl Pyridyl Ketones (5). The ketones were dissolved in benzene (200 ml/g) and treated with excess ethylene glycol and 1.2 equiv of *p*-toluenesulfonic acid. The solution was refluxed using a Dean-Stark trap to collect azeotroped water. The progress of the reaction was monitored by TLC and was complete in 12–48 hr. When the ketone was nearly completely consumed, the solution was cooled and neutralized by addition of sodium bicarbonate and water. When evolution of CO_2 was complete, the mixture was transferred to a separatory funnel. The benzene layer was separated and the aqueous layer was extracted with ether. The combined organic solutions were dried and evaporated. Yields for the individual compounds follow: **5b-2,** 58%; **5b-3,** 51%; **5b-4,** 55%; **5c-2,** 68%; **5c-3,** 70%.

Wolff–Kishner Reduction of 2-Indolyl Pyridyl Ketones to 2-(Pyridylmethyl)indoles (8). The ketone (0.03 mol) was dissolved in a solution containing 10 ml of hydrazine hydrate and 10 g of potassium hydroxide in diethylene glycol. The resulting solution was stirred under a nitrogen atmosphere in an oil bath at 120–140° for 6 hr. The reaction mixture was then diluted with water (~300 ml) and extracted with ether. The ether extracts were dried over potassium carbonate and then evaporated to dryness. Pure products were obtained by crystallization of the residual oils. Yields follow: **8b-2,** 88%; **8b-3,** 92%; **8b-4,** 100%; **8c-3,** 85%.

Chloroacetylpiperidines 7 and 10. In most cases the pyridines were reduced to the corresponding piperidines and then chloroacetylated without full characterization of the intermediate piperidine. To a solution of the pyridine in glacial acetic acid (10 ml/g of reactant) there was added platinum oxide (50–100 mg/g of reactant) and the suspension was shaken under 50 psi hydrogen in a Parr apparatus. The speed of reduction was somewhat variable but was usually complete in 24–48 hr. Periodic monitoring by TLC was done to confirm completeness of reduction. The reaction mixture was then filtered through Celite[15] filter aid. The filtered catalyst was washed with methanol and the filtrate was evaporated to dryness using a rotary evaporator. The residual oil was dissolved in water, neutralized by addition of solid sodium bicarbonate, and extracted with chloroform when evolution of CO_2 was complete. To the chloroform solution there was added solid potassium carbonate and the mixture was stirred vigorously during addition of 1.5 molar equiv of chloroacetyl chloride or chloroacetic anhydride. Reaction was rapid and exothermic with the acid chloride and in a few instances there was an indication of some Friedel–Crafts acylation of the indole ring. Reaction using the anhydride required about 1 hr of stirring at room temperature. When reaction was complete, as judged by TLC, water was added and stirring was continued for 5–15 min to hydrolyze remaining anhydride or acid chloride. The chloroform layer was then separated and dried over potassium carbonate. Evaporation of the solution left the crude product, which was purified by crystallization or chromatography on silica gel. Yields follow: **7a-2,** 89%; **7b-2,** 81%; **7b-3,** 56%; **7b-4,** 72%; **7c-2,** 82%; **7c-3,** 85%; **10b-2,** 31%; **10b-3,** 56%; **10b-4,** 46%; **10c-3,** 33%.

1-Chloroacetylpiperidyl Indolyl Carbinols (4). Two diastereomers of **4b-2** were isolated after a sequence commencing with the ketone **2b-2.** To a solution of **2b-2** (2.36 g, 10 mmol) in methanol (50 ml) containing 1 ml of concentrated hydrochloric acid there was added platinum oxide catalyst (100 mg) and the solution was shaken under 50 psi hydrogen for 4 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residual oil was dissolved in water, neutralized by the addition of excess sodium bicarbonate, and extracted with ether. Chloroacetylation was carried out in the presence of excess solid potassium carbonate using 2 equiv of chloroacetyl chloride. The reaction was complete in 5 min. Water (100 ml) was added and the ether layer was separated, dried, and evaporated. The residue was chromatographed on silica gel (30 g) using toluene–ether for elution. The less polar diastereomer was obtained in 55% yield, mp 142–143°, after recrystallization from ether. The more polar diastereomer was obtained in 18% yield, mp 150–152°, after recrystallization from ether. Compound **4a-4** was obtained via **1a-4.** 1-Benzenesulfonyl-2-lithioindole and 4-pyridinecarboxyaldehyde reacted to give **1a-4** in 36% yield. It was not further purified. To a solution of 5.0 g of **1a-4** in glacial acetic acid (25 ml) there was added 20 mg of platinum oxide. The solution was shaken under 55 psi hydrogen for 72 hr, at which point TLC indicated complete reaction. The solution was filtered and evaporated to leave a glassy residue which was dissolved in water and neutralized with sodium bicarbonate. The alkaline solution was extracted with chloroform and the chloroform was evaporated, leaving 2.77 g of residual **3a-4.** This was acylated in chloroform over solid potassium carbonate to give 1.4 g (overall 24%) of **4a-4,** mp 178–179° after recrystallization from acetone.

2-(1-Methylindolyl) 2-Pyridylmethyl Ketone (11b-2). A solution of 2-methylpyridine (5 ml, ~50 mmol) in ether (20 ml) was treated with 10 ml of 2.2 *N* phenyllithium and the resulting amber suspension was stirred at room temperature for 2.5 hr. A solution of methyl 1-methylindole-2-carboxylate (4.2 g, 22 mmol) in ether (20 ml) was prepared and the suspension of 2-pyridylmethyllithium was then added to it. The resulting mixture was stirred overnight. It was then hydrolyzed with aqueous ammonium chloride and extracted thoroughly with ether. The ether solution was extracted with dilute hydrochloric acid. The acidic solution was made alkaline and extracted with ether. The ether was evaporated and the residue was purified by chromatography on silica gel using 1:1 ether–chloroform for elution. The major product, **11b-2,** was crystallized by trituration with hexane and obtained in 29% yield. A slightly more polar fraction contained the carbinol resulting from addition of two molecules of 2-pyridylmethyllithium to the ester, mp 166–167° after recrystallization from acetone–ether.

Conversion of 11b-2 to 14b-2. The conversion of **11b-2** to **14b-2** by ketalization, reduction, and chloroacetylation was carried out by the same procedures described for the 2 → 5 → 6 → 7 sequence. The overall yield from **11b-2** was 67%.

2-Indolyl 4-Pyridylmethyl Ketone (11c-4). A solution of 10 ml of 4-methylpyridine in ether (40 ml) was treated with 15.0 ml of 2.2 *N* phenyllithium. The solution was stirred at room temperature for 45 min and then added dropwise to ethyl indole-2-carboxylate (2.8 g, 15 mmol) in ether (100 ml). The mixture was stirred overnight and then hydrolyzed with aqueous ammonium chloride and extracted with ether. The extract was dried and concentrated. The residue was chromatographed on silica gel using ether for elution. The fraction containing **11c-4** crystallized from ether–hexane, giving pure ketone, mp 168–169° (31%).

Conversion of 11c-4 to 14c-4. The standard ketalization–reduction–chloroacetylation sequence gave **14c-4** in 17% yield, mp 139–141°.

General Photolysis Conditions. Most of the photolyses were run in dilute solution in methanol. The solutions were purged by a nitrogen stream before (0.5 hr) and during photolysis. In runs in-

volving ketals sodium carbonate was included to neutralize evolved hydrogen chloride and prevent hydrolysis or methanolysis. The photolysis apparatus consisted of a water-cooled quartz immersion well containing a Vycor filter sleeve and a 450-W Hanovia mercury lamp. Times required for photolysis were determined by monitoring the progress of the reaction by TLC. At the completion of the photolysis the solvent was evaporated and the residue was chromatographed on silica gel. Ether or ether–chloroform mixtures were used for elution. Product yields, melting points, and recrystallization solvents are given in Table II. A more detailed description of some of the photolyses follows.

Photolysis of 7c-3. A solution of **7c-3** (1.0 g) in methanol (750 ml) containing sodium carbonate (2.0 g) was irradiated for 20 min. At this point TLC indicated nearly complete disappearance of starting material and the formation of two photoproducts. The methanol was evaporated and the residue was stirred with 1:1 chloroform–ether and applied to a column of silica gel (30 g). The column was eluted with ether. The first component eluted was recovered **7c-3** (73 mg). This was followed by **33** (312 mg, 35%), which crystallized from ether. The third fraction was **34** (83 mg, 9%), obtained as crystals from ether. The final fraction gave 112 mg of the *N*-acetyl analog of starting material.

Photolysis of 4b-2. Both stereoisomers of the carbinol **4b-2** were photolyzed separately and showed identical behavior. A solution of the less polar stereoisomer (922 mg) in methanol (525 ml) was irradiated for 6.7 hr using a 200-W Hanovia lamp as the source. At the completion of the photolysis two products were evident by TLC. The solvent was evaporated and the residue was chromatographed on silica gel using 1:1 toluene–chloroform with gradual addition of ether for elution. The only product which was eluted was **23** (23% yield) obtained as colorless crystals, mp 205–206°, after recrystallization from acetone–ether. Subsequent TLC investigation revealed that **23** had been formed from the initial photoproducts during the evaporation of methanol prior to chromatography. Attempts to isolate the intermediate photoproducts were unsuccessful but it was possible to demonstrate by TLC that each stereoisomer of **4b-2** formed the two photoproducts in approximately the same ratio and that both products were converted to **23** on warming in methanol.

When **23** (16 mg) was refluxed with a solution of potassium carbonate (100 mg) in methanol-*O*-*d* (6 ml) and D_2O (2 ml) for 4 hr the peak due to the CH_2 group disappeared from the NMR spectrum.

Photolysis of 7b-3. A solution of **7b-3** (500 mg) in methanol (750 ml) containing sodium carbonate (250 mg) was photolyzed for 11 min in the standard apparatus, after which time disappearance of starting material was complete. The solvent was evaporated and the residue was chromatographed on silica gel using 1:1 ether–chloroform for elution. Eluted first was **29** (28 mg, 6%). The second fraction contained **28** (97 mg, 23%). The third fraction was **27** (23 mg, 5%) and finally the *N*-acetyl compound (67 mg, 15%) was eluted. When the photolysis was carried out in 1-propanol, little **27** or **28** was formed. The yield of **29** increased to 23% and the *N*-acetyl by-product was formed in 28% yield.

Photolysis of 7a-2. A solution of **7a-2** (700 mg) in benzene (700 ml) was photolyzed for 1.5 hr using the standard apparatus. The reaction solution was washed with aqueous sodium carbonate, dried, and then chromatographed on silica gel. The column was eluted with ether and 1:1 ether–ethyl acetate. The first material eluted was compound **7c-2** resulting from cleavage of the benzenesulfonyl group (147 mg, 29%). There was then obtained 142 mg of recovered starting material. This was followed by a third fraction (130 mg, 19%) which crystallized from ethyl acetate to give **24**, an isomer of the starting material.

Synthesis of Ketone 20 by Polyphosphoric Acid Cyclization. (This synthesis was carried out by D. E. Rearick.) Tryptophyl bromide (334 mg) and ethyl piperidine-2-carboxylate (491 mg) were refluxed in acetonitrile (10 ml) for 22 hr and the solvent was then evaporated. The residue was dissolved in 10% aqueous acetic acid. The solution was filtered and the filtrate was made basic with ammonium hydroxide. The product was extracted with chloroform and obtained as an oil. The oil was dissolved in ethanol (2 ml) and added to 12 ml of barium hydroxide solution. The mixture was refluxed for 7 hr, cooled, and neutralized with 20% sulfuric acid. The precipitated barium sulfate was washed several times with hot water. The combined aqueous solution was evaporated to dryness and further dried by azeotroping with benzene. A final evaporation of the residue from methanol left **19** as a foam (350 mg).

The noncrystalline acid **19** (3.90 g) was ground to a powder and heated with 400 g of polyphosphoric acid at 80–85° for 0.5 hr with frequent stirring. The reaction mixture was then stirred into 1200 ml of ice water and the resulting solution was made slightly basic (pH 9) with concentrated ammonium hydroxide. The resulting precipitate was extracted into chloroform and the combined extracts were dried. The crude product was chromatographed on Florisil (120 g). A fraction containing **20** (1.37 g, 38%) was eluted with chloroform. It was recrystallized from chloroform–hexane to give yellow prisms, mp 172–180° dec.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.64; H, 7.15; N, 11.06.

Conversion of 17 to Ketone 20. The ketal **17** (20 mg) was dissolved in tetrahydrofuran (10 ml) and lithium aluminum hydride (82 mg) was added. The solution was refluxed under nitrogen for 24 hr. The reaction mixture was then diluted with water and extracted thoroughly with chloroform. The total residue (18 mg) was heated with 5 ml of water containing 0.5 ml of concentrated hydrochloric acid for 10 min. The solution was extracted with chloroform and then made alkaline with excess potassium carbonate and extracted with chloroform. The extract contained **20** as indicated by TLC. It was filtered and evaporated, leaving a yellow gum (10 mg), which was dissolved in ether (1 ml). Crystallization gave compound **20** (3.9 mg, 24%) having an infrared spectrum identical with that of **20** prepared by the alternative synthesis.

Ketone 26 by Hydrolysis of 25. A solution of **25** (40 mg) in methanol (2 ml) and water (1 ml) was treated with 1 drop of concentrated hydrochloric acid. The solution was heated on a steam bath for 10 min, diluted with more water, and extracted with chloroform. The residue from evaporation of the chloroform gave **26** (14.6 mg, 40%), mp 146–147°, on crystallization from ether.

Similar procedures were used to convert **16** to **21** (68%), **28** to **30** (100%), **33** to **35** (47%), **34** to **36** (34%), and **29** to **31** (75%). Ketone **22** was isolated directly from a photolysis, probably by inadvertent hydrolysis catalyzed by HCl generated in the photolysis.

Conversion of 35 to 36. A solution of **35** (50 mg) in ethanol (30 ml) was treated with 1 ml of 0.4 *N* sodium ethoxide solution. The solution was stirred for 8 hr at room temperature, at which time TLC indicated that complete conversion to **36** had occurred. The solution was diluted with water and extracted with chloroform. Evaporation of the chloroform left crystalline **36** (40 mg, 80%) having an infrared spectrum identical with that of **36** prepared by hydrolysis of **34**.

The transformation was also monitored by NMR experiments. Addition of 1 drop of 2 *N* NaOD in D_2O to a DMSO-d_6 solution of **35** resulted in the appearance of a spectrum recognized as that of **36** but lacking the doublets at 3.80 and 4.32 ppm which are due to the CH_2 unit between the indole ring and amide carbonyl. Also missing from this final spectrum was the broad signal at 2.88 ppm assigned to the bridgehead proton. A similar experiment but with a eight-fold decrease in NaOD concentration revealed that considerable exchange at the CH_2 group took place prior to any isomerization to **36**.

Methylation of 34 to 28. Sodium hydride (30 mg of 57% mineral oil dispersion) was washed with hexane and then warmed for 0.5 hr with dimethyl sulfoxide (1 ml). To this solution **34** (10 mg) was added and stirred at room temperature for 15 min. Excess (0.5 ml) methyl iodide was then added and the solution was stirred for an additional 15 min. The reaction mixture was diluted with water and extracted with ether. TLC indicated complete conversion to **28**. The ether was evaporated and the residue was redissolved in a small amount of ether. Compound **28** (7.0 mg, 70%), having an infrared spectrum identical with that of **28** prepared by photocyclization of **7b-3**, crystallized.

Isomerization of Ketone 31 to 32. A solution of **31** (12 mg) in ethanol (3 ml) was treated with 1 drop of 2 *N* NaOH. Although TLC with ether on silica gel indicated no change, a plate developed in 3:1 chloroform–acetone showed complete conversion to a second substance in less than 30 min. The solution was diluted with water (2 ml) and concentrated. On standing, **32**, mp 204–205° (7.1 mg, 59%), crystallized.

Methylation of 39 to 37. Sodium hydride (30 mg of 57% mineral oil dispersion) was washed with hexane and then dimethyl sulfoxide was added. The mixture was warmed for 30 min. Compound **39** (5 mg) was added and the solution was stirred for 10 min. There was then added excess (0.5 ml) methyl iodide and the solution was stirred at room temperature for 20 min. The reaction mixture was diluted with water and extracted with ether. Evaporation of the ether left crystalline **37** (4 mg, 80%) having an infrared spectrum and TLC behavior identical with those of **37** prepared by photolysis of **10b-3**.

Reduction of 36 to 39. A solution of **36** (14.6 mg), triethylsilane

(1 ml), trifluoroacetic acid (1 ml), and carbon tetrachloride (1 ml) was refluxed under nitrogen for 3 days. Water was added and then excess sodium carbonate was added to the mixture. The solution was extracted with chloroform and the extract was evaporated to dryness. The residual oil was placed on a column of silica gel and eluted with 1:1 chloroform–ether. Two principal fractions were detected by TLC. The first was evaporated and the residue was crystallized by trituration to give **39** (3.2 mg, 24% yield) having an infrared spectrum identical with that of **39** prepared by photolysis of **10c-3**. The second fraction was 3.1 mg of recovered **36**. There was no indication of the formation of any **40**.

Thermal Stability of 33 and 40. Bis(ethoxyethyl) ether was distilled from sodium metal under nitrogen. Solutions of **33** and **40** (2.0 mg/2 ml) were prepared and portions of the solutions were sealed in Pyrex ampoules. The ampoules were maintained in oil baths at 170° and analyzed by HPLC.

Acknowledgment. The ^{13}C NMR spectrum and some of the 100-MHz spectra were recorded on a Jeol PS-100-P pulse Fourier transform NMR instrument purchased with the aid of National Science Foundation Grant MPS73-08469. The 300-MHz spectra were recorded at the NMR Center, Institute of Polymer Science, The University of Akron, Akron, Ohio.

Registry No.—**1a-4,** 54851-93-3; **1b-4,** 54851-94-4; **2b-2,** 54841-95-5; **2b-3,** 54851-96-6; **4a-4,** 54851-97-7; **4b-2** isomer 1, 54852-27-6; **4b-2** isomer 2, 54852-28-7; **5b-2,** 54851-98-8; **5b-3,** 54851-99-9; **5c-2,** 54852-00-5; **5c-3,** 54852-01-6; **7a-2,** 54852-02-7; **7b-2,** 54852-03-8; **7b-3,** 54852-04-9; **7b-4,** 54852-05-0; **7c-2,** 54852-06-1; **7c-3,** 54852-07-2; **8b-2,** 54852-08-3; **8b-3,** 54852-09-4; **8b-4,** 54852-10-7; **9c-3,** 54852-11-8; **10b-2,** 54852-12-9; **10c-3,** 54852-29-8; **11b-2,** 54852-13-0; **11c-4,** 54852-14-1; **12c-4,** 54852-15-2; **14b-2,** 54852-16-3; **14c-4,** 54852-17-4; **15,** 54852-18-5; **16,** 54852-19-6; **17,** 54852-20-9; **21,** 54852-21-0; **22,** 54852-22-1; **23,** 54852-23-2; **25,** 54852-24-3; **26,** 54852-25-4; **27,** 54852-30-1; **28,** 54910-63-3; **29,** 54852-31-2; **30,** 54852-32-3; **31,** 54852-33-4; **32,** 54910-64-4; **33,** 54852-34-5; **34,** 54910-65-5; **35,** 54852-35-6; **36,** 54910-66-6; **37,** 54852-36-7; **38,** 54910-67-7; **39,** 54852-37-8; **40,** 54852-38-9; 1-methyl-2-lithioindole, 54852-26-5; 1-benzenesulfonyl-2-lithioindole, 40900-03-6; 2-pyridinecarboxaldehyde, 1121-60-4; 3-pyridinecarboxaldehyde, 500-22-1; ethylene glycol, 107-21-1; chloroacetyl chloride, 79-04-9; 2-methylpyridine, 109-06-8; methyl 1-methylindole-2-carboxylate, 37493-34-8; 4-methylpyridine, 108-89-4; ethyl indole-2-carboxylate, 3770-50-1.

Supplementary Material Available. Spectral and analytical data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2613.

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