Conformational Requirements for the Existence of Bohlmann Bands in the Infrared Spectra of Indolo[2,3-*a*]quinolizidines.

I. *cis*- and *trans*-2-*tert*-Butyl Derivatives

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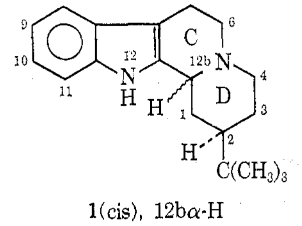
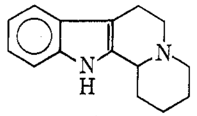
cis- and *trans*-2-*tert*-butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1** and **2**), respectively, are prepared from 3-acetylindole and 4-*tert*-butylpyridine by a sequence involving iodination–alkylation (64%), reductive cyclization (67%), and hydrogenation (94%). Whereas **1**, with a trans C/D ring fusion, shows two Bohlmann bands in the 2800–2700-cm^{-1} region of the infrared spectrum, epimer **2**, with a conformationally pure cis C/D ring fusion, is devoid of absorption in this region.

Quinolizidines having a trans ring fusion show characteristic absorption bands in the 2800–2700-cm^{-1} region of the infrared spectrum.[3,4] These absorptions, termed "Bohlmann bands," result from a specific interaction between the nitrogen lone pair and at least two axial hydrogens on carbons adjacent to the nitrogen atom. Quinolizidines having a cis ring fusion either show much weaker or show no Bohlmann bands, since with this stereochemistry only one α C–H bond can be trans diaxial with the nitrogen lone pair. The theoretical explanation for these low frequency C–H stretching vibrations remains unclear, although it is widely assumed that both specific charge delocalization (hyperconjugation) from the nitrogen lone pair to the axial α C–H bonds and vibrational coupling between two (or three) axial α C–H bonds accounts for the origin of Bohlmann bands.[3,4]

We undertook the present study to establish the conformational requirements for the existence of Bohlmann bands in the indolo[2,3-*a*]quinolizidine system, a structure which forms the basis for the *Corynanthe-Yohimbe* class of indole alkaloids. We were particularly interested in preparing and studying a simple derivative of this system which in one configuration would have a homogeneous cis C/D ring fusion. To this end and because it is clear that small alkyl groups are not sufficient to "lock"[5] a cis C/D ring fusion (*vide infra*), we chose to prepare and study *cis*- and *trans*-2-*tert*-butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine,[6] **1** and **2**, respectively, and compare them with the known, unsubstituted indolo[2,3-*a*]quinolizine **3**.



1(cis), 12bα-H
2(trans), 12bβ-H



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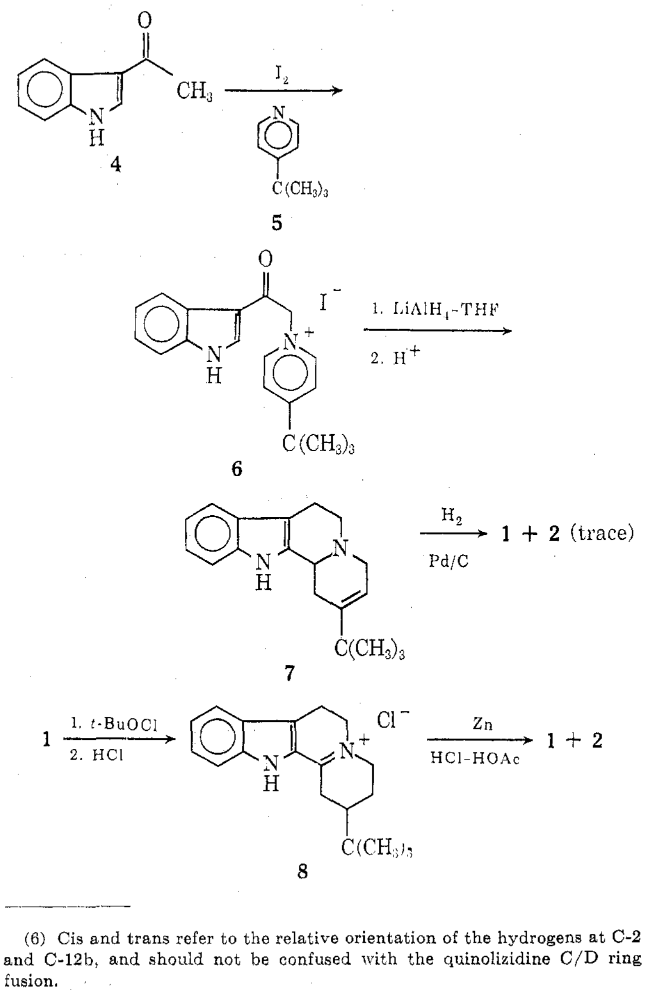
Results and Discussion

Synthesis.—Compounds **1** and **2** are prepared by the general method of Potts and Liljegren,[7] using 3-acetylindole (**4**) and 4-*tert*-butylpyridine (**5**), as summarized in Scheme I.

SCHEME I



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[1] Recipient of a Public Health Service Research Career Development Award (1KO4-GM-23756) from the National Institute of General Medical Sciences, 1971–1976.

[2] NDEA Predoctoral Fellow, 1971–1973.

[3] J. Skolik, P. J. Krueger, and M. Wiewiorowski, *Tetrahedron*, **24**, 5439 (1968).

[4] For a review, see T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971).

[5] The term "lock" refers to the magnitude of the ground-state free energy difference between conformers and does not imply that there is a significant barrier to ring flipping and nitrogen inversion between conformers. Indeed, these processes are rapid at room temperature.

[6] Cis and trans refer to the relative orientation of the hydrogens at C-2 and C-12b, and should not be confused with the quinolizidine C/D ring fusion.

[7] K. T. Potts and D. R. Liljegren, *J. Org. Chem.*, **28**, 3066 (1963).

The iodination–alkylation reaction between **4** and **5** affords **6** in 64% yield. Treatment of **6** with lithium aluminum hydride in tetrahydrofuran followed by acid work-up gives **7** in 67% yield. The position of the double bond in **7** follows from previous work[7,8] and is supported by an intense peak at m/e 170 in the mass spectrum from the dihydro-β-carboline ion arising from a retro Diels–Alder reaction.[8] Hydrogenation of **7** in ethanol over palladium/charcoal gives essentially a single, crystalline compound in 94% yield. Small amounts ($<5\%$) of an amorphous compound can be isolated from the hydrogenation reaction by a combination of column and thick-layer chromatography. This amorphous compound is present to the greatest extent ($\sim5\%$) in hydrogenation reactions carried out in ethanol–ether (70:30). The crystalline and amorphous compounds are assigned structures **1** and **2**, respectively. Compound **2** is more conveniently obtained by treating **1** with *tert*-butyl hypochlorite followed by successive exposure to hydrogen chloride[9,10] and zinc[11] to give a mixture of **1** and **2** in nearly equal amounts, as judged by tlc.

The crystalline compound is assigned the cis configuration **1** and the amorphous compound is assigned the trans configuration **2** on the basis of their nmr and mass spectra. The amorphous material (**2**) exhibits an absorption at 4.44 ppm due to the C-12b proton, while the crystalline material (**1**) shows no saturated proton absorption below 3.3 ppm. This low-field chemical shift for the amorphous compound (**2**) is consistent with a cis C/D ring fusion and is well documented.[4,12–14] For example, this proton in 3-isoajmalicine, an alkaloid with a cis C/D ring fusion, appears at 4.45 ppm.[13]

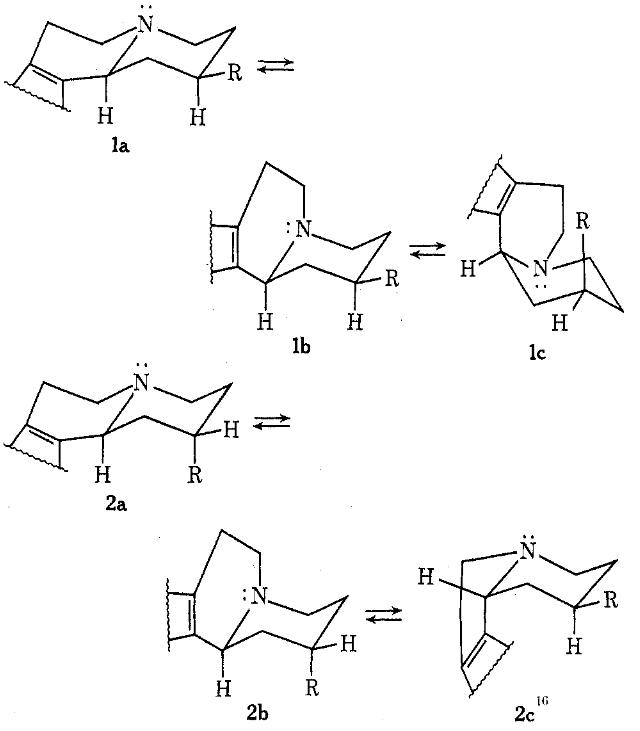
The mass spectra of **1** and **2** are consistent with the assignments. The crystalline epimer (**1**), with a trans C/D ring fusion, shows an M − 1 ion (100%) more intense than the parent ion (87%). The amorphous epimer (**2**), with a cis C/D ring fusion, shows an M − 1 ion (94%) less intense than the parent ion (100%). We interpret this difference as being a consequence of the trans-diaxial orientation of the C-12b hydrogen and the nitrogen lone pair in **1**, which apparently

$$\mathbf{1} \xrightarrow{e^-} \mathbf{8}\ \text{cation} + \text{H}\cdot$$

provides a geometry for efficient loss of the C-12b hydrogen atom.[15]

Conformational and Infrared Spectral Analysis.— The 2-substituted indolo[2,3-*a*]quinolizidine system can exist in six conformations (two configurations), with equilibration by nitrogen inversion and *cis*-decalin ring inversion (Scheme II).

Scheme II



Regardless of the size of the R group in the cis configuration (**1**), conformer **1a** with all substituents equatorial on the D ring will dominate the equilibrium. Conformer **1b** with an ethyl-like axial substituent on nitrogen may contribute about 5% to the equilibrium.[17] The contribution from conformer **1c** with a cis-1,3-diaxial interaction between substituents will be negligible.

It is clear from earlier work with compounds having the trans configuration **2** that the smaller alkyl groups and phenyl are incapable of shifting the equilibrium **2a** ⇄ **2b** ⇄ **2c** exclusively in favor of the cis-fused conformer **2c**. That is, the 2-methyl-,[18a] 2-phenyl-,[18a] and 3-ethylindolo[2,3-*a*]quinolizidine[18b] epimers corresponding to **2** exhibit infrared and nmr spectra consistent with a mixture of **2a** and **2c**.[19] Thus, alkyl substituents in **2** with *A* values of 1.7 (methyl) and 1.8 (ethyl) kcal/mol[20] cannot overcome the thermodynamic stability of the trans C/D quinolizidine ring fusion (*e.g.*, **2a**) which may be 2.6 kcal/mol more stable than the cis C/D ring fusion (*e.g.*, **2c**).[21] A phenyl substituent with an *A* value of 3.1 kcal/mol[20] can shift the equilibrium slightly in favor of **2c** (*i.e.*, $\sim70\%$ of **2c** based on an *A*-value difference of 0.5 kcal/mol).

In contrast to methyl, ethyl, and phenyl, a *tert*-butyl substituent, with its overwhelming equatorial prefer-

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(8) E. M. Fry and J. A. Beisler, *J. Org. Chem.*, **35**, 2809 (1970).

(9) L. J. Dolby and G. W. Gribble, *ibid.*, **32**, 1391 (1967).

(10) W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).

(11) W. F. Trager, J. D. Phillipson, and A. H. Beckett, *Tetrahedron*, **24**, 2681 (1968).

(12) W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.*, **83**, 4816 (1961).

(13) E. Wenkert, B. Wickberg, and C. L. Leicht, *ibid.*, **83**, 5037 (1961).

(14) M. Uskoković, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *ibid.*, **86**, 3364 (1964).

(15) The mass spectrum of a C-12b deuterium-substituted indolo[2,3-*a*]-quinolizidine supports **8** cation as being the main structure of the M − 1 ion: G. W. Gribble, *J. Org. Chem.*, **37**, 1833 (1972).

(16) For clarity, **2c** as illustrated is the enantiomer resulting from the ring inversion of **2b**.

(17) In ethylcyclohexane the axial conformer contributes about 5% based on an *A* value of 1.68 kcal/mol: W. F. Trager, C. M. Lee, and A. H. Beckett, *Tetrahedron*, **23**, 365 (1967), and references cited therein.

(18) (a) J. Gootjes, A. M. De Roos, and W. Th. Nauta, *Recl. Trav. Chim. Pays-Bas*, **85**, 491 (1966); (b) E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, **84**, 4914 (1962).

(19) An alternative, less likely explanation for the observation[18] of Bohlmann bands in configuration **2** (R = Me, Ph) is that the cis-fused conformer **2c** (R = Me, Ph) gives rise to infrared absorption in the Bohlmann region. This explanation cannot be ruled out by the available data and was one of the reasons why we chose to study the unambiguous *tert*-butyl substituted derivative.

(20) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 44, 440.

(21) For quinolizidine itself, the trans fusion is 2.6 kcal/mol more stable than the cis fusion: H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, **No. 59**, 6191 (1968).

ence (*A* value = 5.6 kcal/mol),[20] will force 2 to exist essentially only[5] as the cis-fused conformer **2c** (R = *t*-Bu).[22]

The solution infrared spectrum of **1** shows bands of medium intensity at 2811 and 2751 cm^{-1}. In contrast, the infrared spectrum of **2** is devoid of absorption in this region (Figure 1). The unsubstituted indolo[2,3-*a*]quinolizidine **3**,[15] which is also thought to exist mainly in conformation **1a** (R = H), shows Bohlmann bands at 2807 and 2757 cm^{-1}.

The bands at 2868, 2846, and 2856 cm^{-1} for **1**, **2**, and **3**, respectively, are assigned to the normal CH$_2$ symmetric vibrations and are, of course, common to both trans and cis C/D ring fusions.

From these results we conclude that (1) the infrared Bohlmann region of C/D trans-fused indolo[2,3-*a*]quinolizidines is best described as consisting of but two bands, at *ca.* 2810 and *ca.* 2755 cm^{-1}, the former being slightly more intense, and (2) a conformationally pure C/D cis-fused indolo[2,3-*a*]quinolizidine shows no absorption in the Bohlmann region.

Experimental Section

Melting points were determined with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Routine infrared spectra were obtained using Perkin-Elmer 21, 137, or 337 instruments. Nmr spectra were obtained from either a Varian Associates HA-60-IL or a Perkin-Elmer R-24 spectrometer. Mass spectral data were collected at Harvard University by Mr. J. W. Suggs. Adsorbents for column chromatography were activity III alumina (Merck) and silica gel (J. T. Baker). Adsorbents for thick layer chromatography and thin layer chromatography were silica gel (Merck) and silica gel G (Merck), respectively. The solvent system used was EtOAc–Et$_3$N (95:5) and chromatograms were developed by spraying with a solution of 3% Ce(SO$_4$)$_2$–10% H$_2$SO$_4$ followed by brief heat treatment at 110°. Organic solutions were dried with anhydrous granular K$_2$CO$_3$ and concentrated *in vacuo* with a Büchi rotary evaporator. Microanalyses were performed by Microtech, Skokie, Ill., and PCR, Inc., Gainesville, Fla. Chloroform solutions of **1**, **2**, and **3** were examined on a Perkin-Elmer 21 instrument (path, 0.1 mm) at a concentration of 0.175 *M*.

4-*tert*-Butyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium Iodide (6).—A mixture of 4-*tert*-butylpyridine (**5**) (14.04 g, 0.104 mol) and 3-acetylindole (**4**) (5.40 g, 0.048 mol) was stirred magnetically and heated until solution was achieved. The solution was then treated with iodine (8.75 g, 0.0348 mol) and heated at 95–110° for 1.5 hr. The product began to precipitate after 0.5 hr and the reaction mixture thickened, preventing efficient stirring. After cooling, the dark solid mass was triturated with 95% EtOH, the slurry filtered, and the solid repeatedly treated with 95% EtOH until no red color remained in the filtrate. The pale tan solid was then dried at 100° for 10 min to give 9.93 g of **6** (64%). The analytical sample was recrystallized three times from aqueous EtOH (50%) to give pale white needles, mp 256–257°.

Anal. Calcd for C$_{19}$H$_{21}$N$_2$OI: C, 54.30; H. 5.04; N, 6.67; I, 30.19. Found: C, 54.58; H, 5.29; N, 6.78; I, 30.04.

Pertinent spectral data for **6** are as follows: ir (Nujol) 3175 (N–H), 1656 (C=O) cm^{-1}; uv max (95% EtOH) 214 mμ (log ϵ 4.46), 243 (4.20), 265 (4.13), 305 (4.11).

4-*tert*-Butyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (7).—Compound **6** (30.0 g, 0.072 mol) was added over a period of 40 min to a stirred slurry of LiAlH$_4$ (13.5 g, 0.31 mol) and 1100 ml of anhydrous THF at −40° under nitrogen. A jade green color rapidly appeared as the reaction warmed to room temperature. The system was then refluxed with efficient stirring for 6 hr under N$_2$. After cooling to 0°, H$_2$O was added dropwise to destroy excess hydride. The slurry was stirred and enough 6 *N* NaOH was added to precipitate the aluminum salts (*ca.* 10 ml) to allow for efficient filtration of inorganic materials. The aqueous THF filtrate was treated with 600 ml of concentrated HCl and stirred for 0.5 hr. Making basic with concentrated NH$_4$OH, extraction of the base with CH$_2$Cl$_2$, drying, and removal of solvent provided 13.5 g (67%) of crude product, homogeneous by tlc (R_f 0.5). Recrystallization from Et$_2$O–pentane gave pure material, mp 154.5–155.5°.

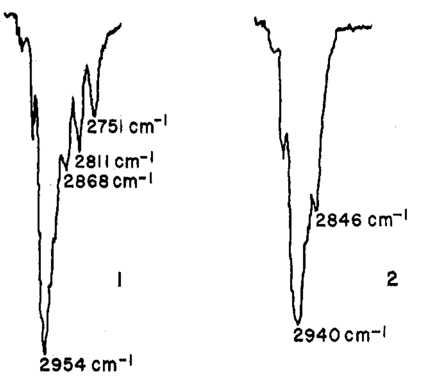

Figure 1.—Infrared spectra (C–H stretching region) of **1** and **2**.

Anal. Calcd for C$_{19}$H$_{24}$N$_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.09; H, 8.63; N, 10.00.

Pertinent spectral data for **7** are as follows: ir (CHCl$_3$) 3463 (N–H), 2961, 2907, 2803, 2742 (C–H) cm^{-1}; uv max (95% EtOH) 233 mμ (log ϵ 4.23), 284 (3.84), 291 (3.77); mass spectrum (70 eV) *m/e* (rel intensity) 280 (49), 279 (36), 233 (35), 170 (100), 169 (89); nmr (CDCl$_3$) δ 7.22 (m, 4 H), 5.53 (t, 1 H, *J* = 2.1 Hz), 1.7–3.8 (m, 8 H), 1.07 (s, 9 H).

***cis*-2-*tert*-Butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (1).**—Compound **7** (1.0 g, 0.0036 mol) was dissolved in a mixture of absolute EtOH containing a trace of Et$_2$O and 0.5 g of 10% Pd/C. Hydrogenation at atmospheric pressure and 25° gave, after filtration, evaporation, and recrystallization of the crude product from Et$_2$O–hexane, 0.94 g (94%) of pure **1**, mp 157–158°. Hydrogenation of a solution of **7** in EtOH–Et$_2$O (7:3) gave a crude product (86% yield) shown by tlc to be a mixture of **1** and **2** (95:5).

Anal. Calcd for C$_{19}$H$_{26}$N$_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.91; H, 9.35; N, 9.76.

Pertinent spectra data for **1** are as follows: ir (CHCl$_3$) 3502 (N–H), 3015, 2954, 2868, 2811, 2751 (C–H) cm^{-1}; uv max (95% EtOH) 227 mμ (log ϵ 4.22), 284 (3.62), 291 (3.55); mass spectrum (70 eV) *m/e* (rel intensity) 282 (87), 281 (100), 225 (61), 226 (14), 170 (5); nmr (CDCl$_3$) δ 6.9–7.8 (m, 4 H), 1.1–3.3 (m, 12 H), 0.92 (s, 9 H).

***trans*-2-*tert*-Butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (2).**—Compound **2** was obtained with difficulty by preparative layer chromatography of the crude hydrogenation mixture of **1**. A more convenient synthesis of **2** involved treating a CH$_2$Cl$_2$ solution of **1** (0.601 g, 0.00213 mol) at 0° with 5 ml of distilled Et$_3$N and adding dropwise under N$_2$ 0.265 g (0.00213 mol) of *tert*-butyl hypochlorite over 5 min. After warming to room temperature, the mixture was stirred for 1 hr and then quenched by the addition of 100 ml of distilled H$_2$O. The organic layer was separated and then washed with 100 ml of distilled H$_2$O. Drying and removal of solvent *in vacuo* gave an oily amber mixture of chloroindolenines. This was treated immediately with 25 ml of 100% EtOH saturated previously with HCl(g) and added to a solution of 150 ml of glacial acetic acid and 25 ml of concentrated HCl. Zn dust (20 g) was added and the suspension (pale green) was refluxed overnight under a N$_2$ atmosphere with efficient stirring. The cooled reaction mixture was decanted from excess Zn and poured into 50 g of ice and 200 ml of concentrated NH$_4$OH. The residual Zn was washed with 25 ml of concentrated NH$_4$OH, and the washings were combined with the aqueous solution. Extraction with CHCl$_3$ followed by drying and evaporation gave 0.45 g (75%) of an amber oil composed of $\sim$55% of **1** and $\sim$45% of **2** as judged by tlc [R_f (blue-green, **1**) 0.68; R_f (blue-green, **2**) 0.37]. Preparative layer chromatography on silica gel with EtOAc (99%)–Et$_3$N (1%) separated the isomers. Two successive separations pro-

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[22] A cyclohexane ring fused onto the D ring, as in the inside yohimbanes, can also be used to control the equilibrium: G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2769 (1967). In this system four configurations are possible and the analysis is somewhat more difficult than it is with monosubstituted indolo[2,3-*a*]quinolizidines.

vided 51 mg of pale amorphous material (**2**), completely homogeneous on tlc.

Anal. Calcd exact mass for $C_{19}H_{26}N_2$: 282.2096. Found: 282.2093.

Pertinent spectral data for **2** are as follows: ir ($CHCl_3$) 3484 (N-H), 3012, 2940, 2846 (C-H) cm^{-1}; uv max (EtOH) 229 mμ (log ϵ 4.21), 283 (3.77), 291 (3.72); mass spectrum (70 eV) *m/e* (rel intensity) 282 (100), 281 (94), 225 (89), 144 (63); nmr ($CDCl_3$) δ 8.06 (s, 1 H), 7.0-7.6 (m, 4 H), 4.44 (t, 1 H), 1.0-3.4 (m, 11 H) 0.9 (s, 9 H).

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Registry No.—**1**, 40587-68-6; **2**, 40587-69-7; **4**, 703-80-0; **5**, 3978-81-2; **6**, 40625-69-2; **7**, 40587-72-2.

Photochemical Conversion of 4-(*o*-Nitrobenzylidene)-4*H*-pyrans to 1-Hydroxy-3-oxospiro[indoline-2,4′-[4′*H*]pyran] Derivatives

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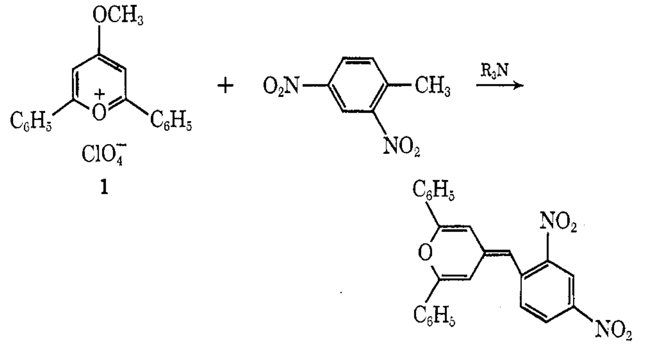
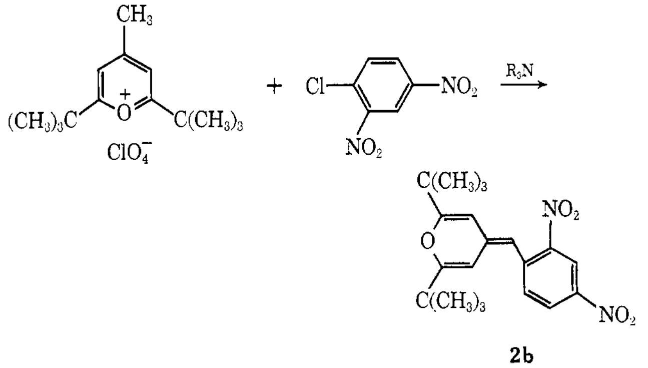
The conversion referred to in the title was investigated for three examples. The structures of the photoproducts were deduced from spectroscopic data and confirmed by chemical transformations.

A variety of compounds have been prepared by the reaction of pyrylium salts with nucleophiles,[1] and we have extended these to include the benzylidenepyran derivative **2a**, which was formed by the reaction of 4-methoxy-2,6-diphenylpyrylium perchlorate (**1**) with 2,4-dinitrotoluene in the presence of a tertiary amine.



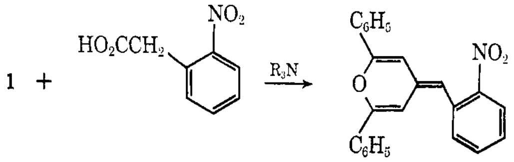
2a

In the course of handling **2a**, it was noticed that both the solid (KBr pressing) and a dilute solution rapidly faded when exposed to room light leading us to investigate this photoreaction. In order to facilitate the interpretation of nmr spectra of the photoproducts, we synthesized the di-*tert*-butyl analog (**2b**),



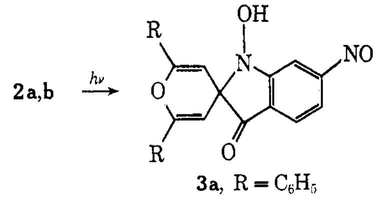
2b

and to simplify the mass spectra and chemical degradation as well as to test the scope of the reaction, we prepared the mononitro derivative **2c** and investigated the photolysis of these three compounds.

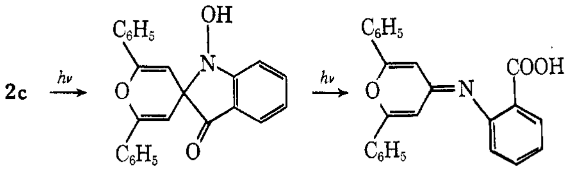


2c

The photolysis of **2a** and **2b** gave products that were isomeric with **2a** and **2b** in nearly quantitative yields. As shown below, structures **3a** and **3b** were assigned to these products. On the other hand, the photolysis of the mononitro compound **2c** yielded, besides the corresponding product (**3c**), another isomeric substance (**4**), which was found to be a photochemical rearrangement product of **3c**.



3a, R = C_6H_5
b, R = $C(CH_3)_3$



3c **4**

The structure of **4** was established through an independent synthesis shown in eq 1.

A number of chemical transformations were carried out on the photoproducts **3a–c** and are summarized in Scheme I. These and the spectroscopic data, discussed below, were used to elucidate the structure of the photoproducts **3a–c**.

Treatment of compounds **3a–c** with perchloric acid gave the benzisoxazole derivatives **6a–c**, which, in

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[1] K. Dimroth, *Angew. Chem.*, **72**, 331 (1960).