1), 104643-19-8; **59** (isomer 2), 104643-20-1; **61**, 104643-21-2; **63**, 104643-22-3; **72**, 104643-29-0; vii, 104643-28-9; viii, 104643-26-7; ix, 104642-96-8; **x**, 104643-25-6; PhCHNPh, 538-51-2; deuterium oxide, 7789-20-0; 1-chloro-3-methyl-2-butene, 503-60-6; acetone, 67-64-1; benzophenone, 119-61-9; azobenzene, 103-33-3; 1-iodobutane, 542-69-8; chlorotrimethylsilane, 75-77-4; (*E*)-2-methyl-2,6-heptadienoic acid, 104643-23-4; (*E*)-2-methyl-2,6-heptadienoyl chloride, 104643-24-5; (*E*)-*N*-methyl-3,*N*-diphenylpropenamide, 33603-46-2; benzaldehyde, 100-52-7; aniline, 62-53-3; (*E,E*)-*N*-methyl-*N*-phenyl-2,4-hexadienamide, 61859-43-6; ethyl sorbate, 2396-84-1; sorbic acid, 110-44-1; sorbic acid chloride, 2614-88-2; *N*-methylaniline, 100-61-8; 3,3-dimethylacryloyl chloride, 3350-78-5; acryloyl chloride, 814-68-6; cinnamoyl chloride, 102-92-1; crotonyl chloride, 10487-71-5.

**Supplementary Material Available:** Experimental details for remaining compounds in this study (13 pages). Ordering information is given on any current masthead page.

# Indolizines. 2. Preparation of 1- and 3-Indolizinols and Their Esters

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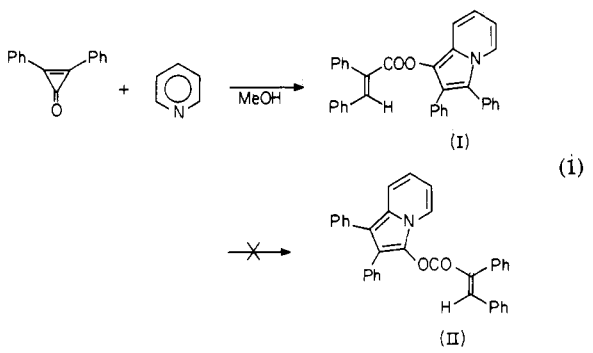
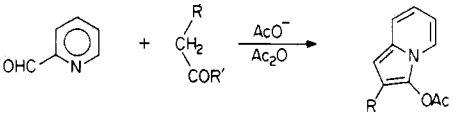
*Received August 18, 1986*

2,3-Diarylcyclopropenones react smoothly with pyridine and substituted pyridines in a variety of solvents to produce 1- and/or 3-indolizinols. The regioisomeric indolizines were characterized by X-ray crystallography of their acetate derivatives. The synthesis and spectroscopic properties of a number of indolizinols and their ester derivatives are described.

The preparation of 1-[(*cis*-2,3-diphenylacryl)oxy]-2,3-diphenylindolizine (I) from pyridine and 2,3-diphenylcyclopropenone (eq 1) was first reported by Breslow et al.[1]

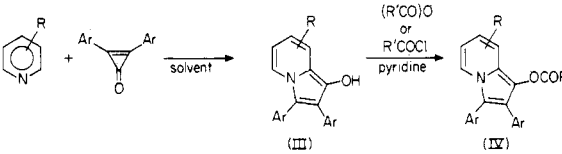



and elaborated on by Lown and Matsumoto.[2] The latter authors assigned the 3-oxy structure II, but we have now established the correct regiochemistry as I by X-ray crystallography[3] and have expanded the reaction to encompass a variety of substituted pyridines and cyclopropenones for the preparation of both 1- and 3-indolizinols. In the extensive indolizine literature, the few reported indolizinols are characterized as unstable intermediates that can be isolated only as esters or salts. Basic hydrolysis of ester I, for instance, furnished *cis*-diphenylacrylic acid but apparently destroyed the unstable indolizinol fragment.[1] In a series of papers, Pohjala[4-6] described the formation (via a Perkin reaction, eq 2) and reactions of some 3-(acyloxy)indolizines but not the isolation or characterization of any of the free indolizinols.




We report here facile, high-yield syntheses of a variety of 2,3-diaryl-1-hydroxyindolizines (III) and their esters (IV), a novel method of preparation of 1,2-diaryl-3-hydroxyindolizines V and their esters VI, and a comparison of NMR chemical shifts and coupling constants.

We have found that pyridines substituted with electron-withdrawing substituents react smoothly with a variety of diarylcyclopropenones to form the corresponding 1-indolizinols III in good yield (eq 3). With the 4-substituted pyridines, near-quantitative yields of the corresponding 7-substituted 1-indolizinols III were formed. The 3-substituted pyridines furnished good yields of ~50–50 mixtures of 6- and 8-substituted indolizinols III, which could be separated by crystallization and/or column chromatography. 2-Substituted pyridines were unreactive, even with prolonged heating. Although all indolizinols substituted with electron-withdrawing groups were reasonably stable in air, they slowly oxidized, forming radical species [as evidenced by a strong ESR signal ($g$ = 2.003 65 ± 0.000 07, $\Delta H$ = 5.6 ± 0.2 G) from an aerated solution of 7-cyano-2,3-diphenyl-1-indolizinol (**32**, free base)].[7] Ad-

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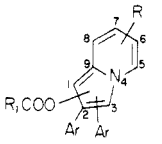
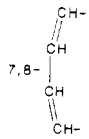
0022-3263/86/1951-4639$01.50/0 

**Table I. Physical and Analytical Data for Diaryl(acyloxy)indolizines (IV, VI)[a]**



| compd | R | (position) $Ar_2$ | $R_1$ | esterification method | mp, °C/ recryst solvent |
|---|---|---|---|---|---|
| 1 | H | (2,3) $C_6H_5$ | $CH_3$ | F | 142/EtOH |
| 2[c,d] | H | (1,2) $C_6H_5$ | $CH_3$ | H | 142–143/EtOH |
| 3 | H | (2,3) $C_6H_5$ | $(CH_3)_3C$ | F | 175–176/MeOH |
| 3a | H | (2,3) $C_6D_5$ | $(CH_3)_3C$ | F | 178–180/$CH_3OH$ |
| 4 | H | (2,3) $p$-$CH_3OC_6H_4$ | $(CH_3)_3C$ | F | 152–153/acetone–$H_2O$ |
| 5 | H | (2,3) $p$-$CH_3OC_6H_4$ | $CH_3$ | F | 156–160/MeOH |
| 6 | H | (2,3) $p$-$(CH_3)_3CC_6H_4$ | $CH_3$ | D | 128–129/ligroin |
| 7[c,d] | H | (1,2) $p$-$(CH_3)_3CC_6H_4$ | $CH_3$ | H | *d* |
| 8 | 7-CH | (2,3) $C_6H_5$ | $CH_3$ | F | 104–105/EtOH |
| 9[b] | 7-$CH_3$ | (1,2) $C_6H_5$ | $CH_3$ | H | |
| 10 | 7-$CH_3$ | (2,3) $C_6H_5$ | $(CH_3)_3C$ | F | 184–187/*i*-PrOH–$H_2O$ |
| 11 | 7-$CH_3$ | (2,3) $p$-$CH_3OC_6H_4$ | $CH_3$ | F | 197–198/EtOH |
| 12 | 8-$CH_3$ | (2,3) $C_6H_5$ | $CH_3$ | F | cannot purify[c] |
| 12a | 6-$CH_3$ | (2,3) $C_6H_5$ | $CH_3$ | F | cannot purify[c] |
| 13 | 7-$CH_3CH_2$ | (2,3) $C_6H_5$ | $CH_3$ | F | 112–113/*i*-PrOH |
| 14 | 7-$C_6H_5CH_2$ | (2,3) $C_6H_5$ | $CH_3$ | F | 147–148/EtOH |
| 15 | 6-CN | (2,3) $C_6H_5$ | $CH_3$ | G | 199/EtOH |
| 16 | 7-CN | (2,3) $C_6H_5$ | $CH_3$ | F | 198–199/EtOH |
| 17 | 8-CN | (2,3) $C_6H_5$ | CH | G | 204–205/EtOH |
| 18 | 7-CN | (2,3) $p$-$CH_2O$-$C_6H_4$ | $CH_3$ | G | 176–177/MeOH |
| 19 | 7-HCO | (2,3) $C_6H_5$ | $CH_3$ | G | 183–184/(MeOH–$H_2O$) |
| 20 | 7-CHO | (2,3) $p$-$CH_3O$-$C_6H_4$ | $CH_3$ | G | 176–178/MeOH |
| 21 | 7-HOCO | (2,3) $C_6H_5$ | $CH_3$ | G | 258–259/EtOH |
| 22 | 7-$CH_3OCO$ | (2,3) $C_6H_5$ | $CH_3$ | D | 173–174/EtOH |
| 23 | 7-$(CH_3)C_3$ | (2,3) $C_6H_5$ | $CH_3$ | F | 186–187/MeOH |
| 24[b] | 7-$(CH_3)C_3$ | (1,2) $C_6H_5$ | $CH_3$ | H | 146–147/MeOH–$H_2O$ |
| 25 | 7-$H_2NCO$ | (2,3) $C_6H_5$ | $CH_3$ | D | 260 dec/EtOH |
| 26 | 7-$CH_3CO$ | (2,3) $C_6H_5$ | $CH_3$ | D | 165–167/MeOH–EtOH |
| 27 |  | (2,3) $p$-$CH_3OC_6H_4$ | $(CH_3)_3C$ | F | 204–206/EtOH |
| 28 | H | (2,3) $(CH_2)_5$ | $CH_3$ | D | 91–92/ligroin |
| 29 | 7-CHO | (2,3) $p$-$CH_3OC_6H_4$ | $p$-$NO_2C_6H_4$ | D | 226–227/EtOH |

[a] All compounds gave correct $m/e$ by field-desorption mass spectrometry (FDMS). Elemental analyses were within acceptable limits (±0.5, C; ±0.3 H; ±0.3, N). [b] Compounds not isolated pure. Preparation described in Table II. Analytical data represent mixture of 1- and 3-acetoxy isomers. [c] Contaminated with 6-$CH_3$ (8-$CH_3$) isomer.

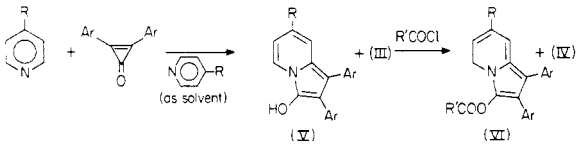
dition of small amounts of L-ascorbic acid as an antioxidant to both the reaction medium and subsequent crystallization solutions adequately protected the products from air oxidation.

In contrast, indolizinols similarly prepared from pyridine or alkylpyridines were very sensitive to oxygen but could be isolated as $HBF_4$ salts or as acyl esters. Stable indolizinols were also easily acylated with acyl chlorides/pyridine or acetic anhydride (eq 3), unlike the azaindolizinols reported by Lown.[2]

Acetylation of 7-methyl-2,3-diaryl-1-indolizinol with acetyl chloride, however, always produced a diacetylated impurity that was difficult to remove. The problem was avoided by using pivaloyl chloride (with its greater steric requirements) as the acylating agent or by acylating with pyridine/acetic anhydride. Table I summarizes preparative and analytical data of the various indolizinol esters.

Surprisingly, neither electronic nor steric effects were important in the reactions of unsymmetrical cyclopropenones with pyridine. 2-(*p*-Anisyl)-3-phenyl-, 2-mesityl-3-phenyl-, and 2-(*p*-anisyl)-3-mesitylcyclopropenones, for instance, all gave nearly equimolar mixtures of the 2,3-diaryl regioisomers of 1-indolizinols.

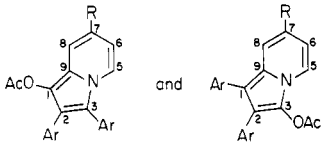
Surprisingly, as we reported earlier,[3] diphenylcyclopropenone in neat pyridine forms the isomeric 1,2-diphenyl-3-hydroxyindolizine in 90% yield (with only a 10% contaminant of 2,3-diphenyl-1-hydroxyindolizine)!



(4)

The isomer ratio of 1-/3-indolizinols obtained from the cyclopropenone–pyridine condensations was remarkably susceptible to substituent effects and large excesses of pyridine (Table II). Such diverse solvents as methylene chloride, dichloroethane, tetrahydrofuran, dioxane, and methanol all gave nearly exclusively the 1-hydroxy isomer with all cyclopropenones and pyridines, even with a five-fold molar excess of the pyridine. With pyridine or 4-alkylpyridine as solvent, however, up to 90% of the 3-hydroxy isomer was formed from 2,3-diphenylcyclopropenone. In contrast, diphenylcyclopropenone in 4-cyanopyridine or 4-pyridinecarboxaldehyde as solvent formed *only* the corresponding 1-hydroxy isomer. Di-*p*-anisoyl- and dimesitylcyclopropenone, on the other hand, with pyridine as solvent also gave nearly exclusively the 1-hydroxy isomer with only a trace of the corresponding 3-hydroxy isomer. Reasons for these differences in isomer

**Table II. Comparison of Ratios of 1- and 3-Acetoxyindolizines (IV, VI) Obtained by Different Condensation Methods**



| method[a] | compd | Ar | R | 1-/3-isomer[b] |
|---|---|---|---|---|
| D | 1, 2 | $C_6H_5$ | H | >95/<5 |
| H | 1, 2 | $C_6H_5$ | H | 23/77[c] |
| D | 6, 7 | 4-$t$-$C_4H_9C_6H_4$ | H | >95/<5 |
| H | 6, 7 | 4-$t$-$C_4H_9C_6H_4$ | H | 19/81 |
| D | 5, 5a | 4-$CH_3OC_6H_4$ | H | 100/0[d] |
| H | 5, 5a | 4-$CH_3OC_6H_4$ | H | >95/<5[d] |
| F | 8, 9 | $C_6H_5$ | $CH_3$ | >95/<5 |
| H | 8, 9 | $C_6H_5$ | $CH_3$ | 11/89 |
| F | 11, 11a | 4-$CH_3OC_6H_4$ | $CH_3$ | 100/0[d] |
| H | 11, 11a | 4-$CH_3OC_6H_4$ | $CH_3$ | >90/<10[d] |
| D | 23, 24 | $C_6H_5$ | $(CH_3)_3C$ | >95/<5 |
| H | 23, 24 | $C_6H_5$ | $(CH_3)_3C$ | 10/90 |

[a] See Experimental Section for descriptions of methods D, H, and F. [b] Product ratios could be easily determined by NMR integrations, as the 1-oxy isomers gave a sharp singlet at $\delta$ 6.5–6.9 and the 3-oxy isomers a sharp singlet at $\delta$ 8.2 in trifluoroacetic acid (protonation at $C_3$). The chemical shifts of the methyl protons of the acetate esters were also different, providing a cross-check on integrations. [c] Dropwise addition of cyclopropenone/$CH_3CN$ to agitated pyridine gave a 1/2 ratio of 10/90. [d] Trace amounts of the 3-isomer were detected by thin-layer chromatography but were not isolated.

ratios are obscure. Factors influencing the position of attack by nucleophiles on a cyclopropenone ring are not completely understood (see ref 8 for a discussion of this phenomenon).

The indolizine ring structure is remarkably stable toward strong acids. 1-(Acyloxy)indolizines, for example, can be hydrolyzed to the indolizinols in quantitative yield by refluxing overnight in aqueous trifluoroacetic acid. Basic hydrolysis, however, rapidly destroys the nucleus, giving a mixture of products.

A comparison of the NMR spectra of the various indolizinols and their esters in chloroform or trifluoroacetic acid (Tables III–V) gives a consistent picture of chemical shifts, coupling constants, and deshielding effects of adjacent and remote substituents, which will be helpful in future structural assignments.

The reaction of cyclopropenones with pyridines provides a versatile synthesis of reactive molecules that have not yet been exploited. Future publications will deal with reactions of these interesting compounds.

## Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. $^1H$ NMR spectra were recorded on a Varian EM-390 spectrometer with $Me_4Si$ as an internal standard in $CDCl_3$ or trifluoroacetic acid (TFA). Infrared spectra (KBr thin films) were recorded on either a Beckman 4250 or a Perkin-Elmer 137 spectrophotometer. Field-desorption mass spectra were obtained on a MAT-731 mass spectrometer. Microanalyses were done by the Analytical Sciences Division, Kodak Research Laboratories, on a Perkin-Elmer C, H, and N analyzer. Solvents and reagents were generally used as received from Kodak Laboratory Chemicals or Aldrich Chemical Company. Some solvents were dried over 3-Å molecular sieves before use.

As reported briefly,[3] structural assignments for the 1- and 3-hydroxy isomers were based on comparison with 1-acetoxy-2,3-diphenylindolizine (1) and 3-acetoxy-1,2-diphenylindolizine (2), whose structures were unambiguously established by X-ray crystallography. Pure colorless crystals of 1 and 2 (experimental methods F and H) were obtained upon cooling ethanol solutions. Crystals of dimensions 0.30 × 0.25 × 0.19 mm (1) and 0.36 × 0.33 × 0.10 mm (2) were used for cell determinations and data collections on an Enraf-Nonius CAD-4 diffractometer equipped with a graphite monochromator and an Mo target X-ray tube ($\lambda$ = 0.7107 Å).

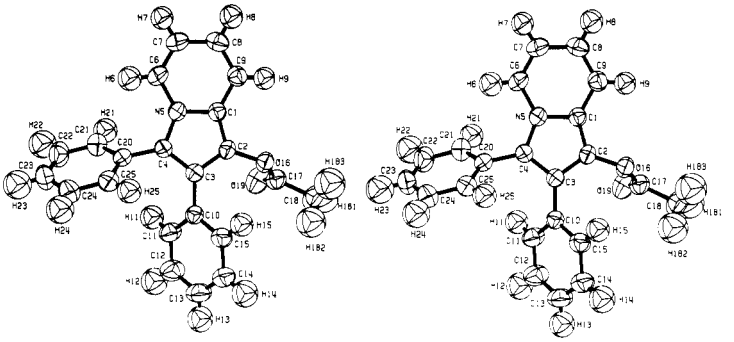


**Figure 1.** Stereoscopic view of 1 with atomic numbering and 50% probability thermal ellipsoids.

The compounds are isomorphous. They crystallize in the centrosymmetric monoclinic space group $P2_1/a$ with $a$ = 17.936 (4) Å, $b$ = 6.470 (3) Å, $c$ = 15.070 (1) Å, $\beta$ = 92.44 (1)°, and $Z$ = 4 [$d_c$ = 1.245 g cm$^{-3}$, $d_m$ = 1.23 g cm$^{-3}$, $\mu$(Mo K$\alpha$) = 0.86 cm$^{-1}$] for 1 and $a$ = 17.698 (4) Å, $b$ = 6.469 (2) Å, $c$ = 15.270 (2) Å, $\beta$ = 92.69 (1)°, and $Z$ = 4 [$d_c$ = 1.245 g cm$^{-3}$, $\mu$(Mo K$\alpha$) = 0.86 cm$^{-1}$] for 2. Equivalent positions in $P2_1/a$, an alternative setting of $P2_1/c$, are $\pm(x, y, z; {}^1/_2 + x, {}^1/_2 - y, z)$.

Intensities were measured at 295 K for $2\theta < 45°$ by a variable scan rate $\omega$–$2\theta$ scan technique. Three reflections that were remeasured periodically showed no significant variation for either compound. The intensities were corrected for background and for Lorentz and polarization effects but not for absorption. The numbers of independent intensities measured were 2278 for 1 and 2265 for 2. Reflections were considered unobserved if $I < \sigma(I)$. Unobserved intensities were set equal to $\sigma(I)$, corrected to $F_{lim}$, and included in the refinements of $F_c > F_{lim}$. The numbers of observed reflections were 1644 for 1 and 1525 for 2.

The structure of 1 was solved by the reiterative application of the Sayre equation.[9-11] An E map revealed 15 atoms; the remaining 10 non-hydrogen atoms were located in a subsequent electron density map. The 17 hydrogen atoms were located from a difference electron-density map after least-squares refinement with anisotropic temperature factors. The starting structure for 2 was taken as the refined structure of 1. The identity of the nitrogen atom in both compounds was established during refinement by the behavior of the temperature factors and of $R_w$.

Refinement was by block-diagonal least squares with 4 × 4 blocks for the hydrogen atoms, which had isotropic temperature factors, and 9 × 9 blocks for the nonhydrogen atoms, which had anisotropic temperature factors.[12] Scattering factors were from a standard compilation.[13] Least-squares weights were taken[14] as $\omega^{-1} = \sigma(F_o) + (0.024F_o)^2$. The refinements converged smoothly to $R$ = 0.041 and $R_w$ = 0.044 for 1726 reflections for 1 and $R$ = 0.043 and $R_w$ = 0.044 for 1624 reflections for 2. Final atomic parameters and structure factors are given in the supplementary material.

Figure 1 is a stereoscopic view[15] of a molecule of 1 showing the

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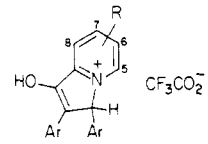
**Table III. Chemical Shifts and Coupling Constants of 2,3-Diaryl-1-hydroxyindolizinium Trifluoroacetates[a,c]**




| | | | NMR chemical shifts ($\delta$) and coupling constants of $CF_3COOH$ salts | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| compd | Ar | R | $H_5$ | $H_6$ | $H_7$ | $H_8$ | $J_{56}$ | $J_{68}$ | $J_{78}$ | $J_{67}$ |
| **30** | $C_6H_5$ | H | 8.55 | 7.70 | 8.50 | 8.20 | 7 | | 7 | 8 |
| **31** | $C_6H_5$ | 7-$CH_3$ | 8.50 | ~7.7 | | 8.20 | 7 | | | |
| **32** | $C_6H_5$ | 7-NC | 8.60 | 7.75 | | 8.35 | 7 | 1.5 | | |
| **33** | $C_6H_5$ | 7-$CH_3CO$ | 8.70 | 8.10 | | 8.65 | 6 | 1.5 | | |
| **34** | $C_6H_6$ | 7-$H_2NCO$ | 8.70 | 8.10 | | 8.65 | 7 | 1.5 | | |
| **35** | $C_6H_5$ | 7-HOCO | 8.70 | 8.25 | | 8.85 | 6 | 1.5 | | |
| **36** | $C_6H_5$ | 7-$CH_3OCO$ | 8.70 | 8.25 | | 8.80 | 7 | 1.5 | | |
| **37** | $C_6H_5$ | 7-HCO | 8.65 | 7.95 | | 8.65 | 6 | 1.5 | | |
| **38** | $C_6H_5$ | 6-NC | 9.05 | | 8.70 | 8.40 | | | 9 | |
| **39** | $C_6H_5$ | 6-$H_2NCO$ | 9.25 | | 9.00 | 8.35 | | | 9 | |
| **40** | $C_6H_5$ | 6-EtOCO | 9.20 | | 9.05 | 8.30 | | | 9 | |
| **41** | $C_6H_5$ | 6-HCO | 9.20 | | 8.95 | 8.40 | | | 9 | |
| **42** | $C_6H_5$ | 8-NC | 8.70 | 7.70 | 8.70 | | 6 | | | 7.5 |
| **43** | $C_6H_5$ | 8-$H_2NCO$ | 8.80 | 7.80 | 9.00 | | 6 | | | 7.5 |
| **44** | $C_6H_5$ | 8-EtOCO | 8.70 | 7.70 | 9.05 | | 6 | | | 8.0 |
| **45** | $C_6H_5$ | 8-HCO | 8.75 | 7.80 | 9.00 | | 6 | | | 7.5 |
| **46** | 4-*t*-$BuC_6H_4$ | H | 8.55 | 7.65 | 8.5 | 8.15 | 7 | 1.5 | 9 | 8 |
| **47** | 4-$CH_3OC_6H_4$ | H | 8.20 | 7.25 | 8.20 | 7.80 | 7 | | 9 | 8 |
| **48**[b] | 4-*t*-$BuC_6H_4$ | 7-HCO | 8.8 | 8.1 | | 8.7 | 7 | 1.5 | | |
| **49** | 4-$CH_3OC_6H_4$ | 7-HCO | 8.75 | 8.05 | | 8.65 | 7 | 1.5 | | |
| **50** | 4-*t*-$BuC_6H_4$ | 7-MeOCO | 8.8 | 8.1 | | 8.7 | 6 | 1.5 | | |
| **51** | 4-*t*-$BuC_6H_4$ | 7-CN | 8.7 | 7.85 | | 8.5 | 7 | 1.5 | | |

[a] Title compounds were prepared, in situ, by using trifluoroacetic acid as solvent. [b] Contained dioxane. [c] Discussion of Table III: As expected, methyl substituents have slight shielding effects on adjacent protons, but electronegative substituents cause deshielding of up to 0.7 ppm (**30**, **31**, and **32**). Alkyl substituents on the 1- and 2-aromatic rings have little effect on chemical shifts of the indolizine protons; however, ep-methoxy substituents can cause considerable upfield shifts (compare **30** and **47**). Coupling constants in the various compounds are nearly the same regardless of substituents.

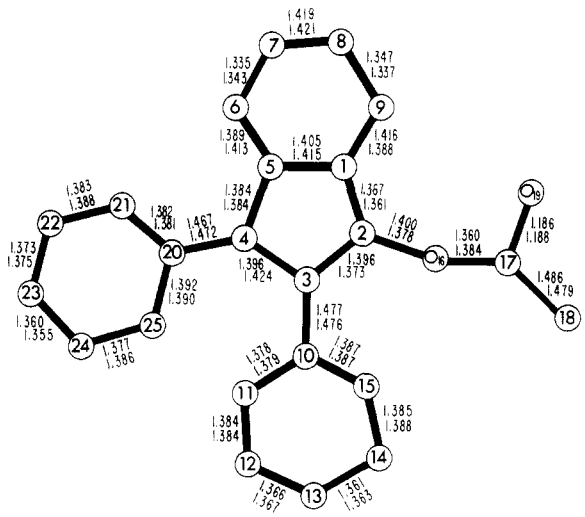


**Figure 2.** Bond lengths of **1** (upper values) and **2** (lower values). Atom 5 is the nitrogen atom in **1**, and atom 1 is the nitrogen atom in **2**. Estimated standard deviations average 0.0032 Å (range 0.0025–0.0041 Å) for **1** and 0.0036 Å (range 0.0028–0.0045 Å) for **2**.

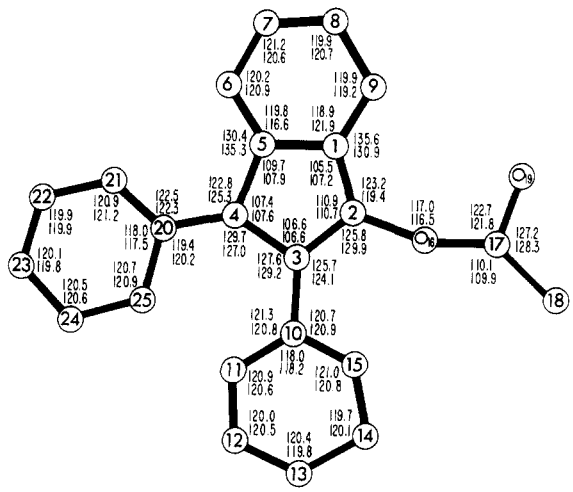


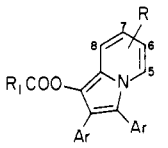
**Figure 3.** Bond angles for **1** (upper values) and **2** (lower values). Atom 5 is the nitrogen atom in **1**, and atom 1 is the nitrogen atom in **2**. Estimated standard deviations average 0.20° (range 0.16–0.25° for **1** and 0.23° (range 0.18–0.28°) for **2**.

numbering system and the thermal ellipsoids. Compound **2** is similar, except that N(5) and C(1) are interchanged. The indolizine rings (atoms 1–9) are only approximately planar, with root mean square deviations of 0.023 Å for **1** and 0.026 Å for **2**. The planes of the substituents are twisted considerably from the indolizine plane, and there is little $\pi$ ovelap between the central rings and the substituent groups. Bond lengths (Figure 2) show that the connecting bonds to the phenyl and acetoxy groups are single bonds.

Bond lengths and angles are shown in Figures 2 and 3. The distances indicate that there is considerable conjugation in the indolizine ring system so that charge-separated canonical structures make important contributions to the bonding.

The bond lengths in the six-membered ring agree exceptionally well for **1** and **2**. The distances in the five-membered ring indicate a high degree of conjugation, which is, however, systematically different for the two compounds. In both **1** and **2** the ring bonds at C(2), to which acetoxy is attached, are shorter by about 0.02 Å than the comparable bonds at the equivalent (relative to N) carbon C(4) in the other compound, to which a phenyl ring is attached. Thus, there is greater double-bond character in the ring bonds around C(2) than in the equivalent ring bonds at C(4) in the other compound. Consideration of possible canonical structures shows that charge-separated structures in which the negative change resides at C(2) must be less important than structures in which the negative charge resides at C(4). This is

**Table IV. NMR Values for 1-(Acyloxy)-2,3-diarylindolizines[a]**




| compd | Ar | R | $R_1$ | NMR data ($\delta$, $CDCl_3$) $H_5$ | $H_6$ | $H_7$ | $H_8$ | R (aH) |
|---|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | H | $CH_3$ | 7.9 | 6.35 | 6.6 | 7.2 | |
| 3 | $C_6H_5$ | H | $(CH_3)_3C$ | 7.9 | 6.3 | 6.55 | 7.1 | |
| 4 | 4-$CH_3OC_6H_4$ | H | $(CH_3)_3C$ | 7.83 | 6.30 | 6.57 | *b* | |
| 5 | 4-$CH_3OC_6H_4$ | H | $CH_3$ | 7.85 | 6.3 | 6.6 | 7.2 | |
| 6 | 4-$(CH_3)_3CC_6H_4$ | H | $CH_3$ | 7.85 | 6.3 | 6.55 | 7.3 | |
| 8 | $C_6H_5$ | 7-$CH_3$ | $CH_3$ | 7.87 | 6.22 | | 6.94 | |
| 10 | $C_6H_5$ | 7-$CH_3$ | $(CH_3)_3C$ | 7.85 | 6.15 | | 6.85 | 2.3 |
| 11 | 4-$CH_3OC_6H_4$ | 7-$CH_3$ | $CH_3$ | 7.75 | 6.15 | | 7.2 | 2.28 |
| 12 | $C_6H_5$ | 8-$CH_3$ | $CH_3$ | 7.75 | (6.1–6.3) | (6.1–6.3) | | 2.45 |
| 12a | $C_6H_5$ | 6-$CH_3$ | $CH_3$ | *d* | *d* | *d* | *d* | 2.24 |
| 13 | $C_6H_5$ | 7-$C_2H_5$ | $CH_3$ | 7.85 | 6.2 | | 6.9 | 2.55 |
| 14 | $C_6H_5$ | 7-$C_6H_5CH_2$ | $CH_3$ | 7.85 | 6.15 | | 7.0 | 3.85 |
| 15 | $C_6H_5$ | 6-CN | $CH_3$ | 8.3 | | 6.65 | 7.3 | |
| 16 | $C_6H_5$ | 7-CN | $CH_3$ | 7.9 | 6.5 | | 7.65 | |
| 17 | $C_6H_5$ | 8-CN | $CH_3$ | 8.05 | 6.4 | 7.1 | | |
| 18 | 4-$MeOC_6H_4$ | 7-CN | $CH_3$ | 8.8 | 6.4 | | 7.6 | |
| 19 | $C_6H_5$ | 7-CHO | $CH_3$ | 7.85 | 6.85 | | 7.7 | 9.79 |
| 20 | 4-$MeOC_6H_4$ | 7-CHO | $CH_3$ | 7.8 | *b* | | 7.65 | 9.79 |
| 21 | $C_6H_5$ | 7-COOH | $CH_3$ | 7.9 | 6.95 | | 8.0 | |
| 22 | $C_6H_5$ | 7-$COOCH_3$ | $CH_3$ | 7.85 | 6.95 | | 7.85 | |
| 23 | $C_6H_5$ | 7-$(CH_3)_3C$ | $CH_3$ | 7.90 | 6.43 | | 7.03 | |
| 25[c] | $C_6H_5$ | 7-$NH_2CO$ | $CH_3$ | 8.80 | 8.17 | | 8.43 | |
| 26 | $C_6H_5$ | 7-$CH_3CO$ | $CH_3$ | 7.86 | 6.95 | | 7.83 | |
| 27 | 4-$CH_3OC_6H_4$ | 7,8-$C_4H_4$ | $(CH_3)_3C$ | 7.65 | 6.55 | | | |
| 28 | 2,3-$(CH_2)_5$ | H | $CH_3$ | 7.56 | (6.2–6.57) | (6.2–6.57) | 7.07 | |
| 29 | 4-$CH_3OC_6H_4$ | 7-CHO | 4-$NO_2C_6H_4$ | 7.95 | *b* | | 7.8 | 9.75 |

[a] Chemical shifts are consistent among the various substituted compounds, relating well to the free alcohols described in Table III. $H_6$ is consistently upfield, and $H_5$, except for 21 and 22, is farthest downfield. $H_6$ and $H_7$ have intermediate chemical shifts, with $H_6$ always farther upfield. The aromatic ester exerts what is probably a neighboring-group effect, giving a downfield shift of 0.2 ppm to $H_8$. [b] Buried under aromatic proton signals. [c] Trifluoroacetic acid (TFA) as solvent; $Me_4Si$ as internal standard. [d] Cannot distinguish from 8-$CH_3$.

**Table V. Comparison of NMR Data of 1- and 3-Acetoxyindolizines**

| compd | solvent | R | NMR chemical shifts (w) 7-$CH_3$ | H from TFA | $H_5$ | $H_6$ | $H_7$ | $H_8$ | $CH_3CO$ |
|---|---|---|---|---|---|---|---|---|---|
| 2 | $CDCl_3$ | H | | | 7.5 | 6.4–6.7 | 6.4–6.7 | 7.5 | 2.3 |
| 1 | $CDCl_3$ | H | | | 7.9 | 6.35 | 6.6 | 7.1 | 2.3 |
| 2 | $CF_3COOH$ | H | | 8.25 | 9.0 | 8.6 | 7.9 | 7.55 | 2.3 |
| 1 | $CF_3COOH$ | H | | 6.95 | 8.5 | 7.75 | 8.6 | 7.9 | 2.6 |
| 9 | $CDCl_3$ | $CH_3$ | 2.2 | | 7.4 | 6.35 | | 7.1–7.3 | 2.3 |
| 8 | $CDCl_3$ | $CH_3$ | 2.3 | | 7.85 | 6.2 | | 6.9 | 2.3 |
| 9 | $CF_3COOH$ | $CH_3$ | 2.7 | 8.15 | 8.8 | 7.3–7.8 | | 7.3–7.8 | 2.3 |
| 8 | $CF_3COOH$ | $CH_3$ | 2.7 | 6.85 | 8.45 | 7.3–7.6 | | 7.75 | 2.65 |
| 23 | $CDCl_3$ | $(CH_3)_3C$ | | | 7.9 | 6.43 | | 7.03 | 2.24 |
| 24 | $CDCl_3$ | $(CH_3)_3C$ | | | 7.51 | 6.62 | | 7.44 | 2.3 |
| 23 | $CF_3COOH$ | $(CH_3)_3C$ | | 6.88 | 8.5 | 7.8 | | 7.88 | 2.63 |
| 24 | $CF_3COOH$ | $(CH_3)_3C$ | | 8.17 | 8.86 | 7.92 | | 7.85 | 2.3 |

undoubtedly an inductive effect caused by the difference in electronegativity of the acetoxy and phenyl groups.

**Preparation of 1-Indolizinols. Method A. For Pyridines Bearing Electropositive Substituents.** A 10% solution of diarylcyclopropenone and an appropriate pyridine (1:1–1:4 molar ratio) in *p*-dioxane containing a small amount of L-ascorbic acid, which had been carefully purged with argon, was refluxed until reaction was complete (when the IR spectrum of the reaction mixture showed no 1850-$cm^{-1}$ band of the cyclopropenone). After addition of excess 10% $HBF_4$, the reaction mixture was evaporated to dryness and washed with water, giving the 1-indolizinol hydrofluoroborate in >90% yields. Products could be recrystallized from methanol/$HBF_4$.

**Method B. For Pyridines Bearing Electronegative Substituents.** An electronegatively substituted pyridine and an equimolar amount of the desired cyclopropenone were dissolved in chlorobenzene, and the solution was refluxed under argon until IR analysis indicated complete reaction. The reaction mixture was diluted with light petroleum and filtered to furnish crude product in >90% yields. Crystallization from an appropriate solvent containing a small amount of ascorbic acid, or column chromatography (silica gel), gave pure materials.

Although most 6- and 8-isomer mixtures required careful chromatography for separation, compounds **37** and **41** (Table III) as free bases were easily separated by dissolving the soluble, purple **41** away from the insoluble, red **37** with methylene chloride.

**Method C. Preparation of 3-Indolizinols.** Since 3-indolizinols were oxygen-sensitive and invariably initially contaminated with 1-indolizinols, pure materials were prepared by acid hydrolysis of the appropriate purified esters (see method H). The ester was dissolved in trifluoroacetic acid containing a little water, and the solution was refluxed overnight. Evaporation of most of the trifluoroacetic acid and flooding of the residue with dilute $HBF_4$ furnished the indolizinol hydrofluoroborates in 80–90% yields. Products were recrystallized from methanol–$HBF_4$.

When desired, 1-indolizinols could also be prepared by this procedure.

**Preparation of Indolizinol Esters. Method D.** Esters of all the indolizinols could be prepared under argon by standard acylation procedures with acyl chlorides and excess pyridine in an appropriate solvent or with pyridine as solvent. However, with 8 (Ar = $C_6H_5$, R′ = $CH_3$) acetyl chloride formed a diacetylated impurity that was difficult to remove.

**Method E.** Indolizinols derived from cyclopropenones bearing electropositive aryl groups (alkoxyphenyl, mesityl, etc.) were prepared rapidly in pyridine under argon and esterified directly without isolation by the addition of a slight excess of acyl chloride or acetic anhydride to the reaction mixture. Reactions were usually complete after 5–10 min of heating on a steam bath. Products were isolated by diluting the reaction mixtures with water (>90% yields).

**Method F.** The esters of oxygen-sensitive indolizinols, which were difficult to obtain free of small amounts of colored contaminants by method D, could be prepared in a purer state by this method. A diarylcyclopropenone, an appropriate pyridine, and an acyl chloride (1:5:2 molar ratio) were dissolved in 1,2-dichloroethane containing a trace of ascorbic acid, and the solution was refluxed under argon for 1–5 h. When reaction was complete (IR analysis), the solvent was evaporated, the residue was washed with water, and the product (80–100% yield) was recrystallized from an appropriate solvent.

**Method G.** The stable indolizinols derived from pyridines with electronegative substituents were dissolved in pyridine and treated with 2 equiv of acetic anhydride, and the solution was heated at 100 °C for 5–10 min. Products were isolated by dilution with water and recrystallized from an appropriate solvent or chromatographed on silica gel (80–95% yields).

**Preparation of 3-Acetoxyindolizines. Method H.** A dilute solution of diphenylcyclopropenone in an appropriate pyridine (see Table II) was refluxed under argon until IR analysis indicated complete reaction. Products were acylated with an appropriate acyl halide or acetic anhydride before isolation. The resulting esters could be isolated and purified by diluting the reaction mixture with water and chromatographing the crude product on silica gel. Best results (highest 3-isomer/1-isomer ratio) were obtained by slow addition of the cyclopropenone to the appropriate pyridine.

**Supplementary Material Available:** Tables VI–XI containing atomic positional and thermal parameters and Tables XII and XIII containing structure factors (10 pages). Ordering information is given on any current masthead page.

# New Synthesis and Spectroscopic Studies of Thialene (Cyclopenta[*b*]thiapyran)[1,2]

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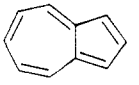
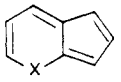
*Received February 17, 1986*

A new five-step synthesis of thialene, cyclopenta[*b*]thiapyran (**2c**), an intensely blue-violet pseudoazulene, is described. The critical final step in the reaction sequence gave 35% yield of the title compound via rapid sequential thermolysis and dehydrogenation of cyclopentano[*b*]-2,4-dihydro-3-(*N*,*N*-dimethyl(thiocarbamoyl))thiapyran (**8**), an intermediate which allowed transient formation of the highly unstable tetrahydro derivative(s). Theoretical and spectroscopic studies of **2c** indicate extensive π-delocalization. The 600.6-MHz $^1$H NMR spectrum displays peaks from 6.78 to 7.84 ppm, confirming a sustained ring current and establishing the molecule as aromatic based on a diatropic definition. The $^1$H-decoupled 75.47-MHz $^{13}$C NMR spectrum displays peaks from 110.01 to 132.09 ppm. The 70-eV EI-MS is startlingly similar to benzo[*b*]thiophene, indicating probable rearrangement to the benzenoid heterocycle prior to fragmentation. The molecule displays weak emission from $S_2$; $\lambda_{max}$ = 338 nm. The IR, (+) and (-) chemical ionization MS, and solvatochromic shifts are reported. The conflict between aromaticity and chemical reactivity is discussed.

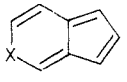
Pseudoazulenes are π-excessive[3] iso-π-electronic heteroanalogues of the nonalternant aromatic hydrocarbon azulene (**1**) derived via substitution for the $C_4$–$C_5$ bond (generating **2**, the [*b*] fused series) or the $C_5$–$C_6$ bond (generating **3**, the "iso" [*c*] fused series).



**1**



**2a**, X=O
**b**, X=NH
**c**, X=S



**3a**, X=O
**b**, X=NH
**c**, X=S

A large number of pseudoazulenes are known;[4] however, work on the unsubstituted parent systems is scarce. Oxalenes **2a** and **3a** are unknown. Pyrindines[5] are thermodynamically less stable than their corresponding prototropic pyridine tautomers[6] and have not been isolated (although a number of N-substituted examples have been reported[6a-c,7]). Isothialene (**3c**) has been the subject of several studies.[7c,d,8] Thialene (**2c**) has been synthesized

(1) Presented in part at the 186th ACS National Meeting, Washington, D.C., August 28–September 2, 1983 [ORGN 0250].

(2) Klein, R. F. X. Ph.D. Dissertation, Georgetown University, Washington, D.C. 20057, August 16, 1985.

(3) Albert defines π-excessive as π-conjugated systems containing more π-electrons than ring atoms; see: Albert, A. *Heterocyclic Chemistry, An Introduction*; Athlone Press: London, 1968. Newkome and Paudler have refined this concept as π-conjugated systems whose MO calculations show that the ground-state electron distribution averaged over all carbons is greater than 1.000 (i.e., benzene); see: Newkome, G. R.; Paudler, W. W. *Contemporary Heterocyclic Chemistry*; Wiley Interscience: New York, 1982.

(4) Timpe, H. J.; El'tsov, A. V. *Adv. Heterocycl. Chem.* **1983**, *33*, 185–239.

(5) Azalene (**2b**) and isoazalene (**3b**) are more commonly IUPAC named as 1*H*-1- and 2*H*-2-pyrindine, respectively.

(6) (a) Anderson, A. G., Jr.; Ammon, H. L. *Tetrahedron* **1967**, *23*, 3601–12. (b) Anderson, A. G., Jr.; Ammon, H. L. *Tetrahedron Lett.* **1966**, 2579–84. (c) Reese, C. B. *J. Am. Chem. Soc.* **1962**, *84*, 3979. (d) Robison, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 6254–7.

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(8) (a) Anderson, A. G., Jr.; Tober, T. Y. *J. Chem. Eng. Data* **1982**, *27*, 99–100. (b) Radeglia, R.; Wagner, R. *Z. Chem.* **1964**, *4*, 145.

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