67.5 MHz) δ 143.7, 131.6, 130.8, 129.8 (C_6H_5), 69.6 ($CHNCH_3$), 59.8 (CH_2SO_2).

2,6-Diphenyl-1,4-dithiane 4,4-Dioxide (13). Hydrogen sulfide gas was passed into a refluxing solution of bisstyryl sulfone (10 g, 0.04 mol) and sodium acetate (10 g, 0.13 mol) in 90% ethanol (200 mL) for 2 h. The reaction mixture was poured into water, and the separated solid material was removed by filtration, washed with water, and recyrstallized from benzene to afford dioxide 13: mp 186 °C (lit.[21] mp 184-85 °C); ^{13}C NMR (CH_2Cl_2, 67.5 MHz) δ 140.2, 131.6, 131.2, 129.9 (C_6H_5), 60.5 (C_2, C_6), 48.5 (C_3, C_5); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.29-7.47 (m, 10 H, C_6H_5), 4.67 (dd, 2 H, C-3,5 C*H*), 3.60 (m, 4 H, $(J_{AX} + J_{BX}) = 14.2$ Hz, C-2,6-CH_2).

(21) Baliah, V.; Anandapadmanabhan, P. *Ind. J. Chem.* 1971, *9*, 1167.

Acknowledgment is made to the National Science Foundation (CHE-8720270), the University of North Carolina—Chapel Hill, and Annamalai University for support of this research.

Registry No. 1, 71989-44-1; 2α, 67530-09-0; 2β, 70561-54-5; 3, 91146-68-8; 4α, 67512-93-0; 4β, 67530-08-9; 5, 34009-06-8; 6, 95158-93-3; 7, 17200-23-6; 8, 18456-45-6; 9, 34379-72-1; 10, 27798-81-8; 11, 135228-17-0; 11·HCl, 135228-20-5; 12, 135228-18-1; 12·HCl, 135228-21-6; 13, 135228-19-2; 14, 62015-76-3; 15, 131814-30-7; 16, 82338-32-7; 1,5-diphenyl-1,4-pentadien-3-one, 538-58-9; *cis*-2,6-diphenyltetrahydrothiopyran-4-one, 18456-44-5; sulfonyldiacetic acid, 123-45-5; benzaldehyde, 100-52-7; bisstyryl sulfone, 4973-50-6; hydrogen sulfide, 7783-06-4.

Indolizines. 5. Preparation and Structural Assignments of Azaindolizinols

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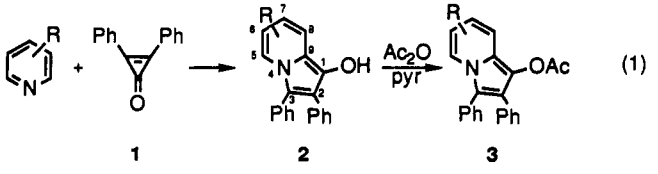
Diphenylcyclopropenone reacts smoothly with a variety of aromatic N-heterocycles to provide aza- and benzazaindolizinols. Although known in the literature, these compounds had been assigned incorrect structures. The preparation and physical properties of a number of derivatives, along with unequivocal assignments of structure based on a variety of NMR techniques, is described herein.

Introduction

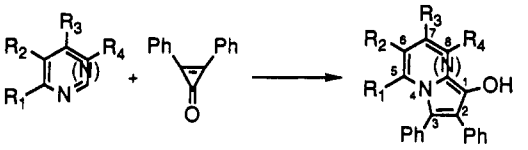
In our papers describing the preparation of 1- and 3-indolizinols and their esters from a variety of pyridines and cyclopropenones,[1,2] we observed that the literature had misassigned the structure of **2** (eq 1, R = H) as a 3-indolizinol.[3,4] Since the structural assignments of many related compounds were subsequently based on the incorrect assignment of **2** as a 3-indolizinol, we felt that a careful reexamination of the structural assignments from the older indolizinol literature using modern NMR techniques was imperative.



(1)

1 **2** **3**

For ease of discussion, and in order to facilitate comparisons of the cyclopropenone/pyridine adducts (indolizinols) with the cyclopropenone/N-aromatic adducts presented herein, the products containing more than one nitrogen in the six-membered ring will be referred to as azaindolizinols and numbered as simple indolizinols (eq 2). Similarly, the adducts derived from bicyclic aromatic



(2)

N-heterocycles will be designated as benzoindolizinols or benzazaindolizinols. The IUPAC numbering and designations for all new compounds are found in the Experimental Section.

In attempts to reproduce the literature azaindolizinols, we were often unable to obtain materials with physical or spectral constants compatible with those described.[3] Since our previous experience has shown that the corresponding esters or ethers of indolizinols are more stable and more crystalline than the free alcohols,[2] we prepared the esters or ethers of the corresponding azaindolizinols (Table I). The use of a nonhydroxylic solvent (method 2, Experimental Section) allowed the direct preparation of the esters in a one-pot operation. Typically, equimolar amounts of diphenylcyclopropenone, **1**, and the appropriate aromatic N-heterocycle were dissolved in dioxane, heated to reflux under argon until the 1850 cm^{-1} IR band of **1** disappeared, and acetylated with a mixture of acetic anhydride/pyridine to yield the azaindolizinol acetates. The corresponding ethers were prepared via the original literature method by treatment of the isolated azaindolizinols with triethyloxonium tetrafluoroborate.[3] In order to demonstrate that the choice of solvent was not a factor in determining the regiochemical outcome of addition products, the free alcohols **7**, **10**, **13**, **15**, and **20** were prepared both in methanol and dioxane and subsequently acetylated to obtain the

(1) Wadsworth, D. H.; Bender, S. L.; Smith, D. L.; Luss, H. R. *Tetrahedron Lett.* 1981, *22*, 3569.
(2) Wadsworth, D. H.; Bender, S. L.; Smith, D. L.; Luss, H. R.; Weidner, C. H. *J. Org. Chem.* 1986, *51*, 4639.
(3) Lown, J. W.; Matsumoto, K. *Can J. Chem.* 1971, *49*, 1165.
(4) Lown, J. W.; Matsumoto, K. *Can. J. Chem.* 1971, *49*, 3119.

0022-3263/91/1956-5594$02.50/0

Table I. Yields and mp's of Azaindolizinols and Azaindolizinyl Acetates

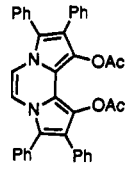
aza-, benzaza-, benzoindolizin-1-ols					acetates[a]		
compd	reactant	mp, °C (lit.[3] mp)	yield[b] (%)	method	compd	mp (°C)	yield[b] (%)
	pyrazine				4[c]	271	75
5	pyridazine	157–158 (158)	87	1	6	159–159.5	85
7	2-methylpyrazine	252–256 dec (263)	45	1	8	163–165	90
		260–265 dec	33	2			
10	2,6-dimethylpyrazine	216–218 (216)	79	1	11	178	81
		218–219	80	2			
13	quinoxaline	298–300 (285)	60	1	14	218–218.5	86
		298–299	60	2			
15	2-methylquinoxaline	240–244 (240)	58	1	16	201–202	95
		243–244	62	2			
18	phthalazine	195–200 dec (187)	86	1	19	211–212	87
20	quinazoline	235–236 (248)	91	1	21	203–204	94
		234–235	78	2			
22	isoquinoline	~130 dec	36	1	23	164–165	82
	quinoline				26	150–151	56
	pyrimidine				28	166–167	32[d]
	pyrimidine				30	141–142	57[d]

[a] In general, the acetate esters were prepared by method 2; however, as noted in the text, they can also be prepared by acetylation of the free alcohols made by method 1. [b] Yields refer to purified, isolated materials. [c] Compound 4 is the bis-acetate of the 2:1 adduct of 1 and pyrazine. [d] Compounds 28 and 30 represent a combined yield of 89% for the reaction of 1 with pyrimidine.

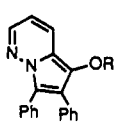
tabulated compounds (Table I). In all cases, the compounds obtained using either solvent were identical in all respects. The regiochemical assignments for the tabulated compounds were best made using a variety of NMR techniques, including ^{1}H NMR, ^{13}C NMR, shift reagents, NOE, and 2D proton–carbon correlation experiments.

Results and Discussion

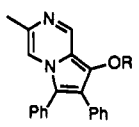
With pyrazine and 1 we were unable to obtain the literature-reported compound. Using the in situ acetylation procedure, we obtained a crystalline product (mp 271 °C), which gave m/e of 576, corresponding to a diacetate of an adduct of 2 mol of 1 per 1 mol of pyrazine. ^{1}H NMR indicated eight different sets of protons, one of which was a sharp singlet at δ 6.98, while ^{13}C NMR showed only 15 different carbons. Irradiation of the acetate methyl only showed an NOE for the ortho protons of the adjacent phenyl group. These spectral data are fully consistent with the symmetrical assigned structure 4.



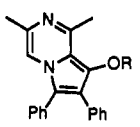
4



5 R = H
6 R = $COCH_3$



7 R = H
8 R = $COCH_3$
9 R = C_2H_5



10 R = H
11 R = $COCH_3$
12 R = C_2H_5

Using method 1, pyridazine and 1 gave a product that was identical with that reported (^{1}H NMR, mp).[3] Method 2 provided the corresponding acetate, in which all carbons and protons were identified by ^{1}H, ^{13}C, and 2D NMR. A 2D NMR (proton–carbon correlation) spectrum of this acetate indicated that C_2 and C_3 were substituted with phenyl groups and H_8 had a three-bond, long-range coupling with C_1, consistent with the assigned azaindolizin-1-ol structure 6. Compound 6 could also be obtained via acetylation (acetic anhydride/pyridine) of the free alcohol prepared by method 1, substantiating our reassignment of 5 as an azaindolizin-1-ol.

2-Methylpyrazine and 1 gave good yields of a 1:1 addition adduct using either method 1 or 2, which was identical with the product reported in the literature (mp, ^{1}H NMR).[3] Treatment of this 1:1 cycloaddition product with acetic anhydride/pyridine provided the corresponding acetate 8. Ethylation of 7 with triethyloxonium tetrafluoroborate provided the ether 9, which was identical (mp, ^{1}H NMR) to the previously reported material.[3] On the basis of the similarity of the ^{1}H NMR spectra of 8 and 11 (from 2,6-dimethylpyrazine, vide infra), we felt confident in assigning 10–12 as azaindolizin-1-ol isomers.[5]

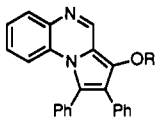
2,6-Dimethylpyrazine and 1 provided an addition product, formulated as 10, which was identical with the literature compound (mp, ^{1}H NMR).[3] The corresponding acetate 11 was prepared both by method 2 and by acetylation of the free alcohol prepared by method 1. In an NOE experiment, irradiation of the C_5 proton of 11 caused an enhancement of the adjacent methyl and the ortho protons of one of the phenyl rings, supporting the assignment of this compound as an azaindolizin-1-ol. Ethylation of 10 gave ether 12, which was identical to the literature compound (mp, ^{1}H NMR).[3]

Quinoxaline and 1 provided an identical product using either method 1 or 2, and although the ^{1}H NMR of this material agreed with that found previously in the literature, the observed mp did not correspond to the reported value.[3,6] Acetylation of material prepared by either method provided identical acetates, and formation of the corresponding ethyl ether occurred readily on treatment with triethyloxonium tetrafluoroborate. Irradiation of the acetate methyl of the acetylated product gave a NOE for the C_8 proton and the ortho protons of the adjacent phenyl

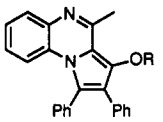
(5) The ^{1}H NMR of the methyl-substituted and methyl-unsubstituted produced were superimposable except for the signals due to the methyl substituent or to the proton it replaced. See supplementary material for spectra.

(6) Our inability to consistently reproduce the data, particularly mp's, reported for the compounds in ref 3 caused us some degree of concern, particularly in light of our structural reassignments of these materials. Perhaps, as Lown alludes to in ref 3, the mp discrepancies can be attributed to varying degrees of keto–enol content of these materials from run to run. The fact that consistently identical compounds are formed using either Lowns method (method 1) or method 2, provides sound evidence for our structural reassignments of these materials.

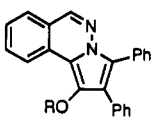
ring, supporting our assignment of structure **14** to this material and our reassignment of **13** and **15** as benzazaindolizin-1-ol isomers. An attempt to prepare the corresponding benzazaindolizin-3-ol through the use of quinoxaline as reactive solvent,[1] followed by in situ acetylation, only resulted in formation of acetate **14**.



13 R = H
14 R = $COCH_3$



15 R = H
16 R = $COCH_3$
17 R = C_2H_5

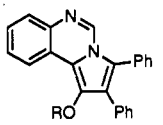


18 R = H
19 R = $COCH_3$

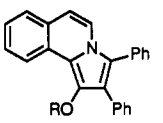
2-Methylquinoxaline and **1** gave an equivalent addition product using either method 1 or 2, which was identical with the literature compound (^1H NMR, mp).[3] This compound and the corresponding acetate were assigned the benzazaindolizin-1-ol structures **16** and **17**, respectively, based on their spectral similarity to those compounds formed from the addition of **1** to quinoxaline.[5]

Treatment of phthalazine with **1** according to either method 1 or 2 provided the same product, which was identical with the literature compound by ^1H NMR, but possessed a mp different than that reported.[3,6] Irradiation of the acetate methyl of the corresponding acetate showed an enhancement of one of the benzo-ring doublets, indicative of structure **19**, and supporting our reassignment of the addition compound of phthalazine and **1** as the benzazaindolizin-1-ol isomer **18**.

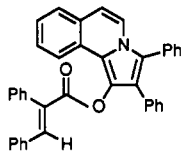
Quinazoline and **1** provided an identical product using either method 1 or 2, with a ^1H NMR spectrum consistent with that reported in the literature, but with a different mp.[3,6] Subsequent treatment of this product with acetic anhydride in pyridine provided the corresponding acetate **21**. Irradiation of the acetate methyl of **21** provided an



20 R = H
21 R = $COCH_3$



22 R = H
23 R = $COCH_3$

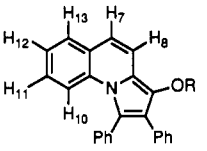


24

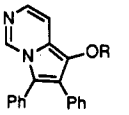
enhancement of one of the benzo-ring doublets and the ortho protons of the adjacent phenyl ring. Coupled with the known propensity of N-3 of quinazoline toward alkylation and addition,[7] compounds **20** and **21** were assigned the depicted benzazaindolizin-1-ol structures, thus reassigning the structure reported previously in the literature.[3] As with quinoxaline, an attempt to prepare the corresponding benzazaindolizin-3-ol through the use of quinazoline as reactive solvent,[1] followed by in situ acetylation, only resulted in formation of acetate **21**.

Treatment of isoquinoline with **1** using method 1 gave varying results. In some cases, the benzoindolizinol **22** was isolated, while in other cases low yields of diphenylacrylate ester **24** were produced. The benzoindolizinol **22** proved to be rather unstable and was best characterized as its correponding acetate, **23**. The ^1H NMRs of **24** and the acetate **23** prepared by method 2 were virtually superimposable, other than differences in the ester proton signals. The literature ^1H NMR data, however, showed significant chemical shift differences for both the C_5 proton and the acrylate vinyl proton from those observed for **24**.[3] Our proposed structures of **22** and **23** as benzoindolizin-1-ol derivatives were supported by NOE experiments. Irradiation of the acetate methyl of **23** caused an enhancement of one of the benzo-ring protons and of the ortho protons of the adjacent phenyl ring, thus supporting our assignment of structure for **22** and **23**. The discrepancies in the ^1H NMRs of Lowns product and **24** could not be resolved. Since it appears that two different diphenylacrylate esters were isolated in low yield, it can be assumed that the reported literature compound was, in fact, a 3-isomer.

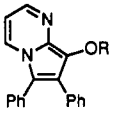
In the course of this work, it was found that some previously unreported cycloadducts could be made. The first of these, compound **25**, could be prepared by the prolonged



25 R = H
26 R = $COCH_3$



27 R = H
28 R = $COCH_3$



29 R = H
30 R = $COCH_3$

reaction of **1** in quinoline as solvent. This new compound was characterized as its acetate **26**, and assignment of all the protons in its ^1H NMR spectra was accomplished via a combination of NOE, shift reagent, and decoupling techniques. The doublet at δ 7.58 is either H_{10} or H_{13}, and irradiation of this proton caused an enhancement of two proximal protons, identifying it as H_{13} and the doublet at δ 7.00 as H_7. Addition of $Eu(fod)_3$ allowed the assignment of the proton proximal to the acetate ester (either H_{10} if the compound is a 3-isomer or H_8 if the compound is a 1-isomer). Decoupling of the proton most shifted on addition of $Eu(fod)_3$ caused the subsequent collapse of the H_7 doublet to a singlet, showing that H_8 is adjacent to the ester and that compound **26** is therefore a benzoindolizin-1-ol isomer as illustrated. Again, as with the quinoxaline and quinazoline adducts (vide supra), this result is in marked contrast to the reaction of **1** with pyridine as reactive solvent, where the indolizin-3-ol is the major constituent of a 9:1 mixture of regioisomers.[1]

Cyclopropenone **1** underwent smooth cycloaddition with pyrimidine (method 2) to afford a mixture of isomeric cycloadducts, which were directly converted to their acetates. The original mixture (~1:2) of acetates was easily separable by silica gel chromatography and characterized as **28** and **30**, respectively, differing only in their direction of ring closure to form the pyrrolopyrimidine products, not in the relative relationship of the oxygen and bridgehead nitrogen. NOE experiments at 500 MHz corroborated our assignments of these materials as isomeric azaindolizin-1-ol derivatives. In the case of **28**, the assignments of the ^1H NMR signals for H_5, H_7, and H_8 were confirmed via decouling experiments.[8] Irradiation of the acetate methyl provided enhancements of the H_8 proton and of the ortho protons on the adjacent phenyl ring. In the case of **30**, irradiation of H_5 showed enhancements of H_6 and of the ortho protons of the adjacent phenyl group. Irradiation of H_7 provided an enhancement of H_6 only, substantiating our assignments of the ^1H NMR spectrum of **30**. These results indicate that **1** adds to pyrimidine to provide two regioisomeric azaindolizin-1-ols, as depicted by **27** and **29**.

In conclusion, in our hands we were unable to prepare any compounds from the addition of diphenylcyclopropenone **1** to various aromatic N-heterocycles that could be identified as having the 3-indolizinol configuration. In the cases of compounds **5**, **7**, **10**, and **16** (and corresponding

(7) See refs 14 and 15 in ref 3 cited above.

(8) This compound exhibited large para coupling (1.5 Hz) between H_8 and H_5 and virtually no meta coupling between H_5 and H_7. This behavior is consistent with ^1H NMR data of 4-substituted pyrimidines: Brügel, W. *Handbook of NMR Spectral Parameters, Vol. II*; Heyden and Son: London, 1979; p 594.

derivatives), we were able to unequivocally reproduce the compounds described in the literature as well as show errors in these literature assignments. We were unable to prepare compounds from pyrazine, quinoxaline, phthalazine, quinazoline, and isoquinoline that displayed properties exactly identical with those previously reported and therefore could neither confirm nor refute their previously assigned structures. However, the structures of the compounds we obtained from the reaction of 1 with these heterocyclic aromatics have been elucidated and in all cases show the exclusive formation of aza-, benzaza-, or benzoindolizin-1-ol compounds. Additionally, three new compounds have been made and characterized as aza- or benzoindolizin-1-ols.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained using a Varian EM-390 (90-MHz) spectrometer with $(CH_3)_4Si$ as internal standard, a General Electric QE-300 (300-MHz) spectrometer, or a Varian VXR-500 (500-MHz) spectrometer. Proton–carbon correlation spectra were obtained on a Bruker AM-500 (500-MHz) spectrometer. ^{13}C NMR spectra were obtained on the General Electric QE-300 (75-MHz) spectrometer or the Bruker AM-500 (125-MHz) spectrometer. Chemical shifts for all NMR spectra are reported in ppm downfield from $(CH_3)_4Si$. Infrared spectra were obtained on either a Beckman 4250 or a Perkin-Elmer 137 spectrophotometer. Field-desorption mass spectra (FDMS) were obtained on a MAT-731 mass spectrometer. Microanalyses were performed by the Analytical Sciences Division, Kodak Research Laboratories. Solvents and reagents were generally used as received from Kodak Laboratory & Research Products or Aldrich Chemical Co.

Except as noted, all new reported compounds were prepared by one of two general methods:

Method 1. This method was designed to duplicate the method of Lown et al. as closely as possible in attempts to prepare the compounds described in the literature.[3] The synthesis of **5** is illustrative.

2,3-Diphenyl-1-hydroxypyrrolo[1,2-*b*]pyridazine (5). A mixture of pyridazine (0.80 g, 10.0 mmol) and **1** (2.06 g, 10.0 mmol) in 20 mL of methanol was purged thoroughly with argon and then refluxed under an argon atmosphere until an infrared spectrum indicated the disappearance of the 1850 cm^{-1} cyclopropenone band (1 h). The mixture was diluted with water and the resulting solid was filtered and recrystallized from methanol to provide 2.0 g (70%) of **5** as a yellow-green solid: mp 157–158 °C (lit.[3] mp 158 °C); ^{1}H NMR (TFA-d_1) δ 9.02 (d, J = 4.7 Hz, 1 H), 8.64 (d, J = 8.6 Hz, 1 H), 8.30 (dd, J = 8.6, 4.7 Hz, 1 H), 7.70–7.60 (m, 2 H), 7.50–7.30 (m, 8 H).

Method 2. This method is an adaptation of our procedure for the preparation of substituted indolizinols[2] and has the advantage of shorter reaction times, avoids the formation of diphenylacrylate esters, and allows in situ acetylation of the initial cycloadducts. The synthesis of **8** is illustrative.

1-Acetoxy-2,3-diphenyl-6-methylpyrrolo[1,2-*a*]pyrazine (8). A mixture of 2-methylpyrazine (0.94 g, 10.0 mmol) and **1** (2.06 g, 10.0 mmol) in 30 mL of *p*-dioxane was purged thoroughly with argon and then refluxed under an argon atmosphere until an infrared spectrum indicated the disappearance of the 1850 cm^{-1} cyclopropenone band (if desired, the free alcohol can be isolated at this stage by precipitation into water or ether, filtration, and drying). The reaction mixture was cooled to room temperature, treated sequentially with pyridine (1.60 g, 20.0 mmol) and acetic anhydride (2.04 g, 20.0 mmol), and then heated to reflux for 10 min. After being cooled, this mixture was poured with rapid stirring into 500 mL of water and the resulting solid was filtered and recrystallized from methanol/water to furnish 2.8 g (78%) of **8** as a white solid: mp 163–165 °C; ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1 H), 7.64 (s, 1 H), 7.45–7.15 (m, 10 H), 2.35 (s, 3 H), 2.32 (s, 3 H); IR (KBr) 1762, 1623, 1416, 1203 cm^{-1}; FDMS m/e 342. Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.92; H, 5.35; N, 8.17.

1-Acetoxy-2,3-diphenylpyrrolo[1,2-*b*]pyridazine (6): mp 159–159.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (dd, J = 4.3, 1.5 Hz, 1 H), 7.62 (dd, J = 9.1, 1.5 Hz, 1 H), 7.50–7.20 (m, 10 H), 6.53 (dd, J = 9.1, 4.3 Hz, 1 H), 2.28 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.6, 142.0, 132.2, 130.7, 130.1, 129.8, 128.3, 128.0, 127.6, 126.9, 124.4, 124.2, 124.0, 119.5, 117.3, 109.5, 20.5; IR (KBr) 1770, 1625, 1504, 1206 cm^{-1}; FDMS m/e 328. Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.57; H, 5.02; N, 8.51.

2,3-Diphenyl-1-hydroxy-6-methylpyrrolo[1,2-*a*]pyrazine (7): mp 260–265 °C dec (lit.[3] mp 263 °C); ^{1}H NMR (TFA-d_1) δ 8.71 (s, 1 H), 7.72 (s, 1 H), 7.55–7.18 (m, 10 H), 2.38 (s, 3 H).

6,8-Dimethyl-2,3-diphenyl-1-hydroxypyrrolo[1,2-*a*]pyrazine (10): mp 216–218 °C (lit.[3] mp 216 °C); ^{1}H NMR (TFA-d_1) δ 7.56 (s, 1 H), 7.50–7.40 (m, 3 H), 7.40–7.30 (m, 3 H), 7.30–7.22 (m, 2 H), 7.22–7.15 (m, 2 H).

1-Acetoxy-6,8-dimethyl-2,3-diphenylpyrrolo[1,2-*a*]pyrazine (11): mp 178 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1 H), 7.40–7.15 (m, 10 H), 2.68 (s, 3 H), 2.31 (s, 3 H), 2.27 (s, 3 H); IR (KBr) 1767, 1626, 1443, 1397, 1202 cm^{-1}; FDMS m/e 356. Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.21; H, 5.70; N, 7.83.

1,2-Diphenyl-3-hydroxypyrrolo[1,2-*a*]quinoxaline (13): mp 298–300 °C (lit.[3] mp 285 °C); ^{1}H NMR (TFA-d_1) δ 8.81 (s, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.65–7.15 (m, 13 H).

3-Acetoxy-1,2-diphenylpyrrolo[1,2-*a*]quinoxaline (14): mp 218–218.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.71 (s, 1 H), 7.92 (d, J = 8.2 Hz, 1 H), 7.50–7.05 (m, 13 H), 2.32 (s, 3 H); IR (KBr) 1762, 1617, 1459, 1382, 1370, 1207 cm^{-1}; FDMS m/e 378. Anal. Calcd for $C_{25}H_{18}N_2O_2$: C, 79.35; H, 4.79; N, 7.40. Found: C, 79.01; H, 4.84; N, 7.34.

1,2-Diphenyl-3-hydroxy-4-methylpyrrolo[1,2-*a*]quinoxaline (16): mp 243–244 °C (lit.[3] mp 240 °C); ^{1}H NMR (TFA-d_1) δ 7.75–7.30 (m, 14 H), 3.24 (s, 3 H).

3-Acetoxy-1,2-diphenyl-4-methylpyrrolo[1,2-*a*]quinoxaline (17): mp 201–202 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 1 H), 7.50–6.95 (m, 13 H), 2.75 (s, 3 H), 2.26 (s, 3 H); IR (KBr) 1765, 1611, 1478, 1400, 1368, 1201 cm^{-1}; FDMS m/e 392. Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.36; H, 5.27; N, 7.04.

2,3-Diphenyl-1-hydroxypyrrolo[1,2-*a*]phthalazine (18): mp 243–244 °C (lit.[3] mp 187 °C); ^{1}H NMR (TFA-d_1) δ 9.6–9.4 (m, 1 H), 9.29 (s, 1 H), 8.5–8.3 (m, 3 H), 7.7–7.2 (m, 10 H), 6.80 (s, 1 H, exchangeable).

1-Acetoxy-2,3-diphenylpyrrolo[1,2-*a*]phthalazine (19): mp 211–212 °C; ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 1 H), 7.93 (d, J = 8.2 Hz, 1 H), 7.70–7.65 (m, 2 H), 7.50–7.20 (m, 11 H), 2.35 (s, 3 H); IR (KBr) 1763, 1603, 1360, 1205 cm^{-1}; FDMS m/e 378. Anal. Calcd for $C_{25}H_{18}N_2O_2$: C, 79.35; H, 4.79; N, 7.40. Found: C, 78.90; H, 4.95; N, 7.43.

2,3-Diphenyl-1-hydroxypyrrolo[1,2-*c*]quinazoline (20): mp 235–236 °C (lit.[3] mp 248 °C); ^{1}H NMR (TFA-d_1) δ 9.29 (s, 1 H), 8.60 (d, J = 8.0 Hz, 1 H), 7.86 (t, J = 8.0 Hz, 1 H), 7.77 (d, J = 8.0 Hz, 1 H), 7.70–7.40 (m, 11 H).

1-Acetoxy-2,3-diphenylpyrrolo[1,2-*c*]quinazoline (21): mp 203–204 °C; ^{1}H NMR ($CDCl_3$) δ 8.67 (s, 1 H), 7.91 (dd, J = 6.4, 2.2 Hz, 1 H), 7.78 (dd, J = 7.0, 2.0 Hz, 1 H), 7.55–7.15 (m, 12 H), 2.35 (s, 3 H); IR (KBr) 1762, 1373, 1348, 1216, 1197 cm^{-1}; FDMS m/e 378. Anal. Calcd for $C_{25}H_{18}N_2O_2$: C, 79.35; H, 4.79; N, 7.40. Found: C, 79.00; H, 4.93; N, 7.32.

1-Acetoxy-2,3-diphenylpyrrolo[1,2-*a*]isoquinoline (23): mp 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 1 H), 7.76 (d, J = 7.5 Hz, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.50–7.20 (m, 12 H), 6.64 (d, J = 7.5 Hz, 1 H), 2.35 (s, 3 H); IR (KBr) 1761, 1602, 1371, 1354, 1207 cm^{-1}; FDMS m/e 377. Anal. Calcd for $C_{26}H_{19}NO_2$: C, 82.74; H, 5.07; N, 3.71. Found: C, 82.64; H, 5.23; N, 3.66.

(*Z*)-2,3-Diphenyl-1-pyrrolo[1,2-*a*]isoquinolinyl 2,3-diphenylacrylate (24): 16% yield; mp 176–177 °C (lit.[3] mp 178 °C); ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 7.4 Hz, 1 H), 8.01 (s, 1 H), 7.76 (d, J = 7.6 Hz, 1 H), 7.60–7.10 (m, 23 H), 6.64 (d, J = 7.6 Hz, 1 H); IR (KBr) 1728 cm^{-1}; FDMS m/e 541.

1-Acetoxy-2,3-diphenylpyrrolo[1,2-*c*]pyrimidine (28): mp 166–167 °C; ^{1}H NMR ($CDCl_3$) δ 8.80 (d, J = 1.5 Hz, 1 H), 7.45–7.20 (m, 11 H), 7.10 (dd, J = 7.0, 1.5 Hz, 1 H), 2.28 (s, 3 H); IR (KBr) 1765, 1623, 1602, 1548, 1425, 1343, 1201 cm^{-1}; FDMS m/e 328. Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.53; H, 5.03; N, 8.45.

1-Acetoxy-2,3-diphenylpyrrolo[1,2-*a*]pyrimidine (30): mp 141-142 °C; ^{1}H NMR ($CDCl_3$) δ 8.24 (dd, J = 7.3, 1.3 Hz, 1 H), 8.08 (dd, J = 3.6, 1.3 Hz, 1 H), 7.45-7.20 (m, 10 H), 6.47 (dd, J = 7.3, 3.6 Hz, 1 H), 2.33 (s, 3 H); IR (KBr) 1765, 1602, 1510, 1440, 1368, 1208, 1074, 769 cm^{-1}; FDMS m/e 328. Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.68; H, 5.09; N, 8.45.

1,10-Diacetoxy-2,3,8,9-tetraphenylpyrrolo[1,2-*a*]pyrrolo-[1,2-*c*]pyrazine (4). A solution of pyrazine (0.40 g, 5.0 mmol) and **1** (2.06 g, 10.0 mmol) in 20 mL of *p*-dioxane was refluxed under argon for 20 min. When the solution was cooled, a crystalline precipitate separated and was filtered to afford the free diol of **4**. This material was directly treated with acetic anhydride (2.04 g, 20 mmol) in 10 mL of pyridine, and the mixture was heated at 100 °C for 10 min. The mixture was poured into water, and the resulting precipitate was filtered and recrystallized from methanol to provide compound **4** (2.16 g, 75%) as a pale tan solid: mp 271 °C; ^{1}H NMR ($CDCl_3$) δ 7.40-7.17 (m, 20 H), 6.98 (s, 2 H), 2.25 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.2, 131.5, 130.0, 129.2, 128.9, 128.0, 127.4, 127.3, 127.2, 125.8, 123.0, 118.4, 112.0, 108.3, 20.2; IR (KBr) 1770, 1360, 1175 cm^{-1}; FDMS m/e 576. Anal. Calcd for $C_{38}H_{28}N_2O_4$: C, 79.15; H, 4.89; N, 4.86. Found: C, 78.66; H, 5.01; N, 4.78.

3-Acetoxy-1,2-diphenylpyrrolo[1,2-*a*]quinoline (26). Diphenylcyclopropenone **1** (1.02 g, 5.0 mmol) was added to 10 mL of quinoline that had been thoroughly purged with argon for 5 min. This mixture was heated at 90 °C until an infrared spectra indicated the disappearance of the 1850 cm^{-1} cyclopropenone band. Acetic anhydride (1.02 g, 10.0 mmol) and pyridine (0.8 g, 10.0 mmol) were then added, and the mixture was warmed at 90 °C for 10 min. The reaction mixture was then dripped into a large volume of dilute HCl and the precipitated produced filtered off and recrystallized from methanol/water to provide 1.06 g (56%) of **26** as a yellow solid: mp 150-151 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 1 H), 7.50-7.00 (m, 15 H), 2.28 (s, 3 H); IR (KBr) 1763, 1604, 1360, 1199 cm^{-1}; FDMS m/e 377. Anal. Calcd for $C_{26}H_{19}NO_2$: C, 82.74; H, 5.07; N, 3.71. Found: C, 82.51; H, 5.26; N, 3.59.

Preparation of Azaindolizinol Ethers. The preparation of the azaindolizinol ethers **9**, **12**, and **15** were performed similarly to the literature procedure.[3] The preparation of **9** is illustrative.

2,3-Diphenyl-1-ethoxy-6-methylpyrrolo[1,2-*a*]pyrazine (9). A suspension of **7** (0.3 g, 1.0 mmol) in 10 mL dry methylene chloride was purged with argon. The mixture was treated with 2 equiv of triethyloxonium tetrafluoroborate (1 M in methylene chloride, 2.0 mL, 2.0 mmol), whereupon the mixture became homogeneous. This was stirred at room temperature for 30 min and washed with dilute Na_2CO_3 and water, and the organic layer was dried over $MgSO_4$. Concentration in vacuo provided 0.33 g (100%) of crude product, which was recrystallized from methanol/water to provide pure **9**: mp 158 °C (lit.[3] mp 157 °C); ^{1}H NMR ($CDCl_3$) δ 8.80 (s, 1 H), 7.54 (s, 1 H), 7.50-7.10 (m, 10 H), 3.95 (q, J = 7.0 Hz, 2 H), 2.32 (s, 3 H), 1.29 (t, J = 7.0 Hz, 3 H).

6,8-Dimethyl-2,3-diphenyl-1-ethoxypyrrolo[1,2-*a*]pyrazine (12): 77% yield; mp 124-126 °C (lit.[3] mp 62 °C);[9] ^{1}H NMR ($CDCl_3$) δ 7.45-7.10 (m, 11 H), 3.73 (q, J = 7.0 Hz, 2 H), 2.81 (s, 3 H), 2.27 (s, 3 H), 1.22 (t, J = 7.0 Hz, 3 H).

1,2-Diphenyl-3-ethoxy-5-methylpyrrolo[1,2-*a*]quinoxaline (15): 83% yield; mp 155-156 °C (lit.[3] mp 152 °C); ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 7.9 Hz, 1 H), 7.45-7.10 (m, 11 H), 7.03-6.90 (m, 2 H), 3.77 (q, J = 7.0 Hz, 2 H), 2.90 (s, 3 H), 1.25 (t, J = 7.0 Hz, 3 H).

Supplementary Material Available: Difference NOE spectra for relevant compounds, HETCOR 2D NMR spectra for **6**, and ^{1}H NMR spectra of the Eu(fod)$_3$ shift reagent experiment of **26** (23 pages). Ordering information is given on any current masthead page.

(9) Compound **12** was observed to partially melt at 60-65 °C and then resolidify and remelt sharply at 124-126 °C.

Palladium-Mediated Synthesis of C-5 Pyrimidine Nucleoside Thioethers from Disulfides and Mercurinucleosides

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Thioether-linked side chains can be created at C-5 of pyrimidine nucleosides via a palladium-mediated reaction of mercurated nucleosides with organic disulfides. 5-(Chloromercuri)-2′-deoxyuridine reacts with butyl disulfide, phenyl disulfide, dimethyl 3,3′-dithiodipropionate, and *N,N′*-bis(trifluoroacetyl)cystamine to yield respectively 5-(1-thiapentyl)-2′-deoxyuridine, 5-(phenylthio)-2′-deoxyuridine, 5-[3-(methoxycarbonyl)-1-thiapropyl]-2′-deoxyuridine, and 5-[3-(trifluoroacetamido)-1-thiapropyl]-2′-deoxyuridine in yields ranging from 46 to 73%. Other mercurated nucleosides, including 5-(chloromercuri)-2′-deoxycytidine, 5-(chloromercuri)cytidine, and 5-(chloromercuri)tubercidin react with *N,N′*-bis(trifluoroacetyl)cystamine and lithium-palladium chloride in methanol to yield the corresponding coupled products, but the yields are much lower (5-10%). The nucleoside coupling reaction is complicated by competing side reactions between disulfides and Pd^{2+}, which remain to be elucidated.

Introduction

Nucleic acid components modified at C-5 of pyrimidine occur frequently in nucleic acids. Hypermodification at C-5 occurs in the DNA of bacteriophages such as SP-15 (*Bacillus subtilis*),[1] T-even phages (*Escherichia coli*),[2-4] and φω-14 (*Pseudomonas acidovorans*).[5] C-5 methylation of specific deoxycytidines in DNA playes a role in recognition and function of DNA binding molecules. At least nine different C-5-modified uridines occur in tRNA.[6] 2′-Deoxyuridine analogues having substituents at C-5 such as ethyl, iodo, propenyl, and bromoethenyl are selective anti-herpes agents.[7] C-5-substituted 2′-deoxyuridine monophosphates, having relatively small but highly elec-

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