Syntheses and Photophysical Properties of Some 5(2)-Aryl-2(5)-(4-pyridyl)oxazoles and Related Oxadiazoles and Furans

(The Late) J. Herbert Hall and Joseph Yuming Chien†
Department of Chemistry and Biochemistry in the Graduate School,
Southern Illinois University, Carbondale, IL 62901, USA

Joel M. Kauffman*, Peter T. Litak and Jeffrey K. Adams††
Department of Chemistry, Philadelphia College of Pharmacy and Science
600 South 43rd Street, Philadelphia, PA 19104-4495, USA

Ronald A. Henry and Richard A. Hollins
Chemistry Division, Research Department, Naval Weapons Center
China Lake, CA 93555, USA
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A number of 5-aryl-2-(4-pyridyl)oxazoles, a 2-aryl-5-(4-pyridyl)oxazole, the related oxadiazole and furan, several 2-(4-pyridyl)cycloalkano[*d*]oxazoles, and many of their quaternary salts were prepared. No single standard synthesis was effective for preparation of more than a few of the 25 free bases described; methods often unique to a base were employed. Minor variations in structure sometimes produced large differences in absorption and emission wavelengths, as well as in the magnitude of the extinction coefficient. The salts are of interest as laser dyes, scintillation fluors, biological stains, and shifters for luminescent solar concentrators.

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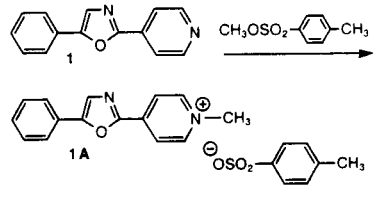
Introduction.

The work at Los Alamos Scientific Laboratories on scintillation fluors resulted in the preparation of 5-phenyl-2-(4-pyridyl)oxazole **1** (Figure 1) and its highly fluorescent quaternary salt with methyl *p*-toluenesulfonate **1A** ("tosylate" or "Ts") [1]. Lee and Robb reported on the lasing properties of **1A** [2], and obtained a patent. Beginning under the direction of Fletcher, Naval Weapons Center, a large number of derivatives were prepared, and evaluated as flashlamp pumped laser dyes. A *p*-methoxy substituent on the 5-phenyl group (see **2** in Table 1) gave some quaternary salts with unprecedented service lifetimes as laser dyes, which have been reported elsewhere [3].

Figure 1. Structure and Quaternization of 5-Phenyl-2-(4-pyridyl)oxazole



The beneficial effects of ring-bridging to force coplanarity and enhance resonance interaction on the lasing properties of oligophenylenes [4] prompted us to attempt the preparation of a number of 2-(4-pyridyl)cycloalkano[*d*]oxazoles in which the 5-aryl ring is fused to C4 of the oxazole ring. The photophysical properties of their quaternary salts have been reported elsewhere [5].

Lastly we investigated the photophysical properties of the related 2-aryl-5-(4-pyridyl)oxazole **14**, the oxadiazole **15**, and the furan **16**, along with their quaternary salts. These properties, as well as the details of syntheses of all the compounds, are now presented.

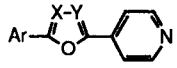
Discussion and Results

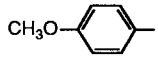
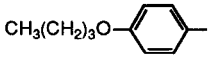
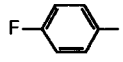
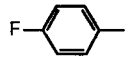
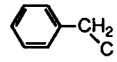
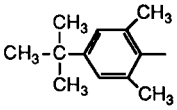
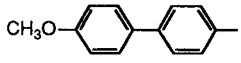
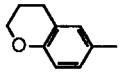
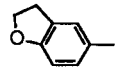
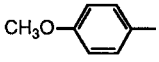
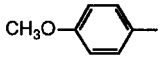
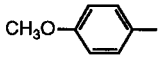
Syntheses of 5-Aryl-2-(4-pyridyl)oxazoles and Related Compounds.

A one step synthesis of 1,3-oxazoles was reported recently [6] by the reaction of ketones with nitriles in the presence of copper(II) trifluoromethylsulfonate as an oxidizing agent. The known model compounds **59a-c** (Figure 2) were prepared to work out the experimental details. In a typical procedure the ketone was added dropwise during 20-90 minutes to the copper(II) trifluoromethylsulfonate [7] in refluxing nitrile containing a trace of *p*-toluenesulfonic acid catalyst, followed by 0-20 minutes of further heating. In the case of **59a** and **59b** the oxazoles were isolated by thermalizing the copper(I) complexes at 200-250° under vacuum and distilling out the product, yields 35 and 45% respectively. In the case of **59c** the complex was destroyed

Table 1

Structures and Absorption and Fluorescence Emission Spectra for 5(2)-Aryl-2(5)-(4-pyridyl)oxazoles and Related Compounds

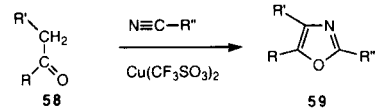


No.	Ar	X	Y	λ max Abs [a]	ε x 10^{-3}	λ max Em [b]	SS [c]
2		CH	N	333 nm 351	23.9 13.5	362 nm *382* 398	49 nm
3		CH	N	—	—	—	—
4		CH	N	318 [d] 322 [e] 372 [f]	— — —	394 [d] 396 [e] 480 [f]	76 74 108
5			N	—	—	—	—
6			N	331 [d] 380 [f]	— —	416 [d] 493 [f]	85 113
7			N	322 [d] 318 [e] 380 [f]	— — —	408 [d] 464 [e] 522 [f]	86 146 142
8			N	—	—	—	—
9			N	—	—	—	—
10		CH	N	—	—	—	—
11		CH	N	—	—	—	—
12		CH	N	—	—	—	—
13		CH	N	—	—	—	—
14		N	CH	325	32.5	350 *365* 382	40
15		N	N	300	25.0	*350* 363	50
16		CH	CH	338 355	33.7 23.0	365 *383* 400	45

[a] Only the longwave bands related to the S_0—S_1 transition are given. Solvent was cyclohexane unless otherwise noted. [b] Determined on Perkin-Elmer LS-5B and are uncorrected unless otherwise noted. Solvent was cyclohexane. Max λ Fl Em is in italics type. [c] SS = Stokes' Shift: major or middle λ Fl Em minus major or middle λ Abs. [d] This is actually λ max Fl Exc in ethanol. [e] This is actually λ max Fl Exc in 1:1::ethanol:water. [f] This is actually λ max Fl Exc in 0.5 M perchloric acid in ethanol.

during steam distillation of the excess benzonitrile, yield 53%. Attempts to use a 1:1 molar ratio of ketone to nitrile in ethyl acetate at room temperature, or in refluxing glyme, or in refluxing diglyme all failed; ketone was recovered. Extended reaction times resulted in the formation of polymeric materials. Attempts were made to react deoxybenzoin with the nitrile germane to this work, isonicotinonitrile. On mixing with copper(II) trifluoromethylsulfonate the nitrile formed an insoluble purple complex. On prolonged refluxing the purple complex disappeared and was replaced with a yellow solid, however, on workup the ketone was recovered, and no oxazole **59d** was obtained. It appears that the use of this method is limited to those cases where the nitrile can be used as the solvent. Turchi's recent monograph on oxazoles [8] cites the cyclodehydration of 2-acylaminoketones first as a method for synthesis of 2,5-diaryloxazoles which may also contain substituents in the 4-position. This is the method we employed for oxazoles **2-4**, **10**, **12-14**, **17-18**, and **21** (attempted, see Figures 3, 4, 7, 8 and 10). In some cases the 2-acylaminoketones were not isolated: oxazoles **2**, **19**, **20**, **21** (attempted), and **22-25** (see Figures 3 and 8).

Figure 2. Studies on Oxazole Synthesis from Condensation of Nitriles with Ketones



a. R=C_6H_5, R'=C_6H_5, R"=CH_3
b. R=CH_3, R'=C_6H_5, R"=CH_3
c. R=C_6H_5, R'=C_6H_5, R"=C_6H_5
d. R=C_6H_5, R'=C_6H_5, R"= 4-pyridyl

Figure 3. Syntheses of 5-(4-methoxyphenyl)-2-(4-pyridyl)oxazole 2 and Its Zwitterionic Quaternary Salts 2J and 2L as an Example of the Phenacylammonium Route

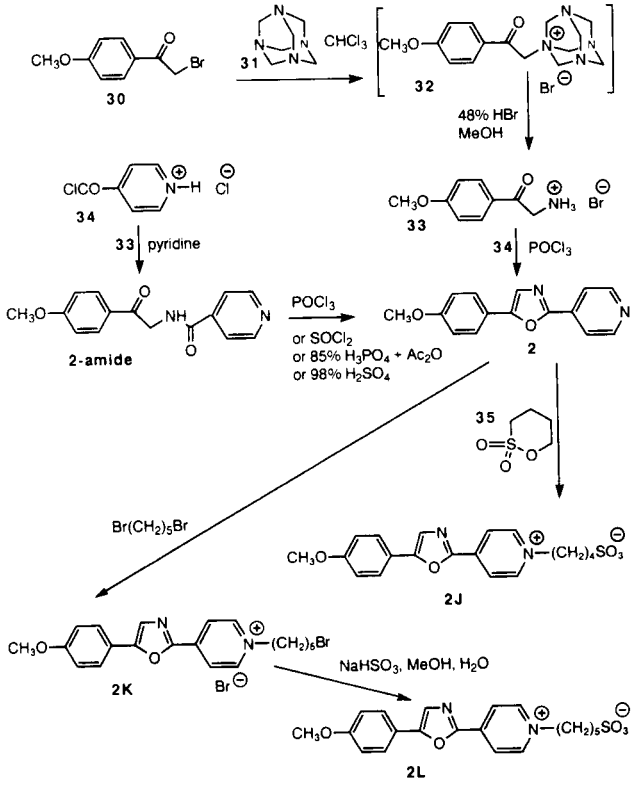


Figure 4. Synthesis of 2-(4-methoxyphenyl)-5-(4-pyridyl)oxazole 14 and Its Quaternary Salt 14A, an Example of the Ketal-Amine Route

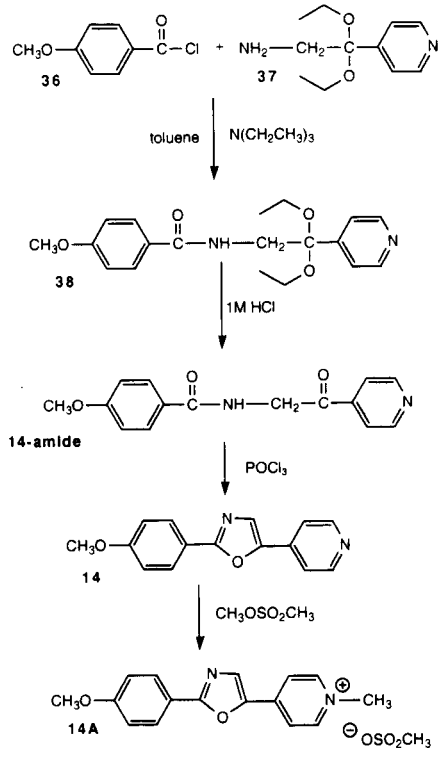
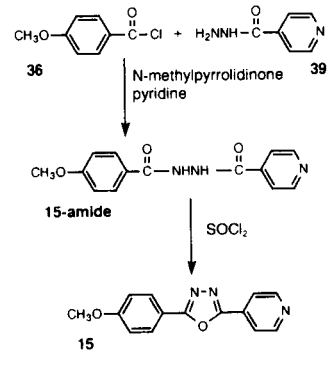


Figure 5. Synthesis of 2-(4-Methoxyphenyl) -5-(4-pyridyl)oxadiazole 15



The 2-aminoketones or phenacylamines from which the 2-acylaminoketones are made are stable only as the acid salts, such as hydrochlorides, and benefit from the presence of excess acid to prevent decomposition on recrystallization. Two main methods were used to prepare the phenacylamine hydrochlorides: (1) the

Figure 6. Synthesis of 2-(4-Methoxyphenyl)-5-(4-pyridyl)furan **16**

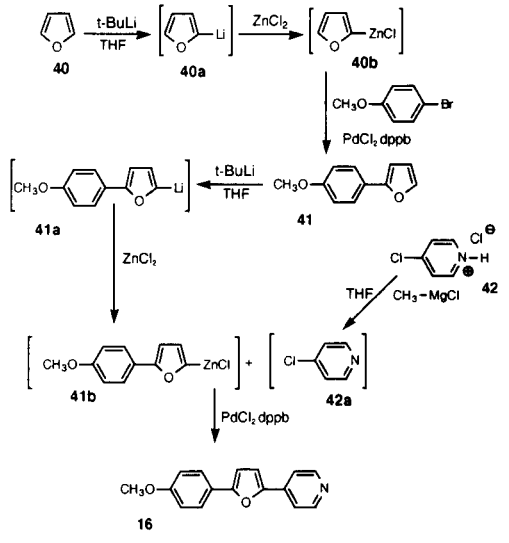


Figure 7. Syntheses of 2-(4-Pyridyl)-4,5-dihydronaphtho[1,2-d]-1,3-oxazole **17** and its 6-Methoxy Derivative **18**, an Example of the Oxime Route

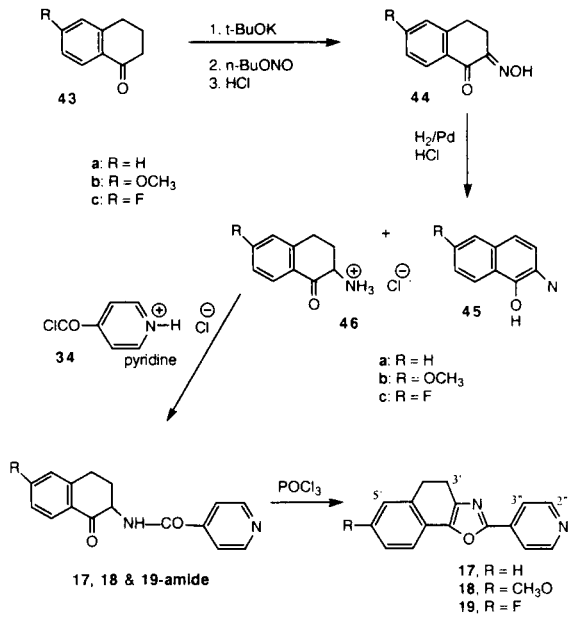


Figure 8. Attempted Synthesis of Naphtho[9,10-d]-1,3-oxazole **21** and Its Diels-Alder Addition Product

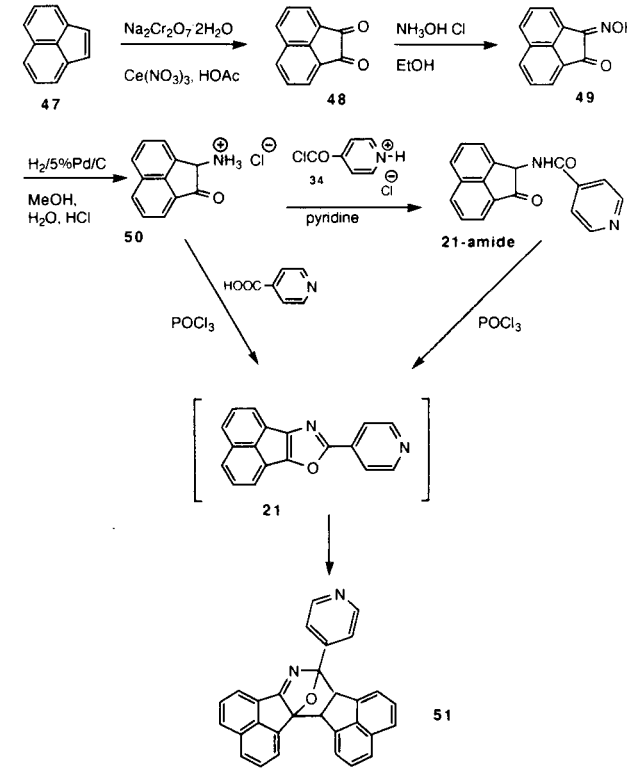
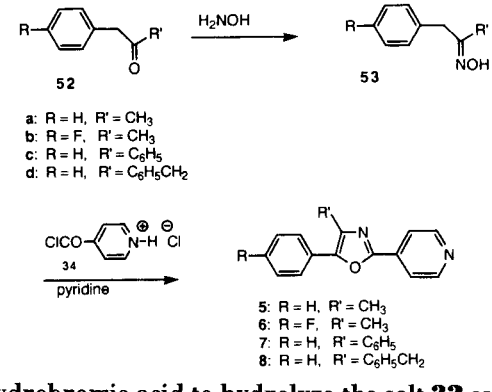
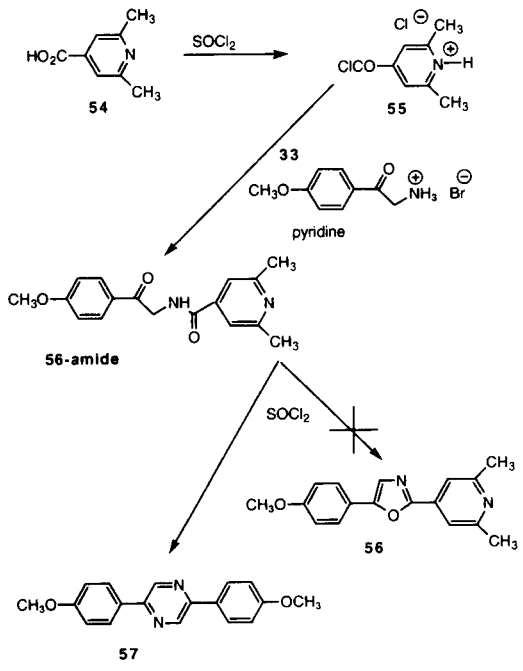


Figure 9. Syntheses of 5-Aryl-2-(4-pyridyl)-4-substituted-oxazoles **5**, **6**, **7**, and **8** as an Example of the Oxime Ester Rearrangment Route



Delépine reaction of a phenacyl halide (this is the sequence **30** + **31** —> **32** —> **33** in Figure 3), and (2) catalytic hydrogenation of 2-oximinoketones (this is the sequence **43** —> **44** —> **46** in Figure 7). The Delépine reaction was superior when the phenacyl halide contained no β-hydrogen that could participate in a dehydrohalogenation. Where a β-hydrogen was present in any of the cyclic ketones, catalytic hydrogenation of 2-oximinoketone was employed. The Delépine reaction with phenacyl bromide **30** with use of hydrobromic acid to hydrolyze the salt **32** avoided a mixture of anions resulting from the use of hydrochloric acid, and allowed advantage to be taken of the insolubility of ammonium bromide in propanols and butanols for easy purification. As an alternative, the reported [9] reaction of acetophenone with ammonium formate was applied to 4-methoxyacetophenone to obtain colorless 1-(4-methoxyphenyl)ethylamine in 50% yield. This was rearranged according to a reported method for this exact compound [10] with use of *t*-butyl hypochlorite

Figure 10. Attempted Synthesis of 2-(2,6-Dimethyl-4-pyridyl)-5-(4-methoxyphenyl)oxazole



to give a 60% yield of 4-methoxyphenacylammonium hydrochloride; still inferior overall to the Delépine reaction. The 2-oximinoketones were prepared either by nitrosation of a ketone with α-hydrogens according to Reifenrath and Fries [11], or by monooxime formation from diketones. Palladium-catalyzed hydrogenations in a Parr apparatus were carried out in a mixture of an alcohol, water, and hydrochloric acid to obtain the stable hydrochlorides. The presence of water was essential for rapid and complete reductions, and this finding has not been reported in the literature.

The direct preparation of oxazoles from isonicotinic acid and a phenacylammonium hydrohalide was reported by Afanasiadi [12] after this work began. Oxazole **2** was reported by Afanasiadi in 65% yield, mp 110°; we obtained 72%, mp 108-109° by this method, but the impurity was very difficult to remove. Our best sample of oxazole **2** from dehydration of **2**-amide with sulfuric acid had mp 112.5-114.5°, and showed a single spot on tlc. Oxazoles **19**, **20** and **22-25** were prepared by us by this "direct" method in 89% (crude), 35%, 1.4%, 2.6%, 72% (crude) and 13% respectively. This indicates that the 2-step method involving isolation of the 2-acylaminoketone is generally superior.

The 2-acylaminoketones or isonicotinamides were invariably prepared from isonicotinoyl chloride and the phenacylammonium hydrohalide in pyridine in fair to good yields. Of the many dehydrating agents known [8] we tried phosphorus oxychloride, thionyl chloride, acetic anhydride with phosphoric acid, and sulfuric acid at room temperature; the last was the best in the one case observed, especially in terms of easy purification of the oxazole **2**.

The 4-substituted oxazoles **5-8** were prepared by a general method [13] involving an electrocyclic rearrangement of the isonicotinate esters of oximes (Figure 9). The identity of oxazole **8** was confirmed as the 4-benzyl-5-phenyl isomer based on the similarity of the absorption and fluoresence maxima of its quaternary salt **8A** (Table 3) to those of the 4-methyl-5-phenyl compound "Ox 20" in [5].

Oxazole **9** was prepared uniquely from oxazole **1** by chlorinating the oxazole with *t*-butyl hypochlorite; the product precipitated from chloroform as the hydrochloride salt.

Oxazole **10** was obtained by dehydration of its 2-acylaminoketone as usual; however the Delépine reaction was not used to make the phenacylamine hydrochloride, probably because steric hindrance prevents reaction of the phenacyl halide with the bulky hexamine. Instead, we followed the reported procedure [14] for 2',4',6'-trimethylphenacyl bromide: reaction of it with potassium phthalimide gave the *N*-alkylphthalimide, which was partially hydrolyzed by

Table 2. Structures of 2-(4-pyridyl)cycloalkano[d]oxazoles and Numbering Used for PMR Assignments

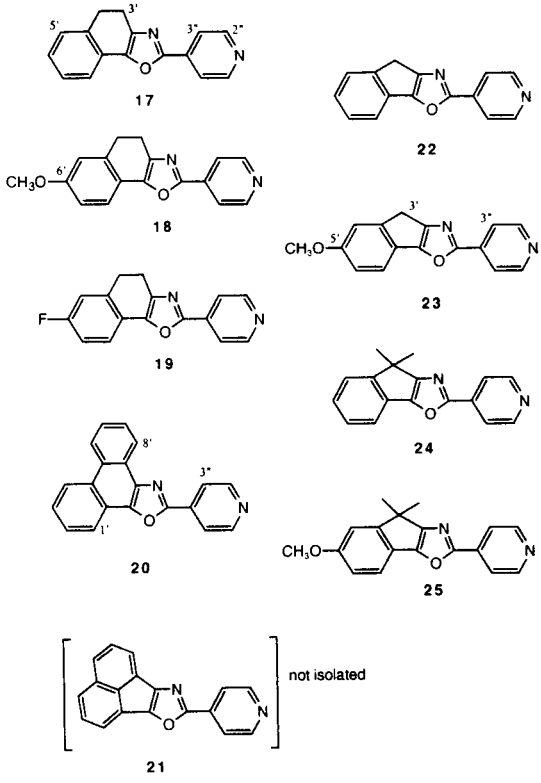
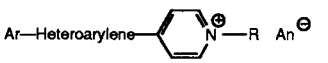


Table 3

Preparative Details for Pyridinium Salts



No. [a]	R	An	Rxn Solv, Vol [b] /Time	Recryst Solv, [c]	Yield	MP	Elemental Assay: Calculated/Found % C	% H	% Other
1B	$-CH_2C_6H_4CN \cdot 3H_2O$ [d]	Br	$Cl(CH_2)_2Cl$,-/24 [e]	95% ethanol, 110	88%	260-262°	54.99/55.23	4.82/4.94	N, 8.36/8.28
1C	$-CH_2C_6H_4OCH_3$	Cl	acetonitrile	not needed	71	228-229	–	–	N, 7.40/7.36
1D	$-CH_2C_6H_4OCH_3 \cdot 1/2\ H_2O$	ClO_4	[f]	not needed	–	200-202	58.48/58.62	4.46/4.43	N, 6.20/6.25
1E	$-CH_2C_6H_4CH{=}CHC_6H_5 \cdot H_2O$	Cl [g]	$Cl(CH_2)_2Cl$,-/24	acetonitrile	≈ 30	235.5-236.5	74.27/74.96	5.39/5.46	N, 5.97/6.01
2A	$-CH_3$	Ts [h]	toluene, 20/1	not needed	71	191.5-193	60.52/60.87	5.30/5.44	N, 6.14/6.18
2B	$-CH_3$	Ms [i]	toluene, 40/2	1-butanol, 10	55	219-221	56.34/56.37	5.01/5.31	S, 8.85/9.02
2C	$-CH_3$	CF_3SO_3	toluene, 55/2.5 [j]	1-butanol, 60	79	227.5-229	49.04/50.17 [k]	3.63/3.65 [k]	–
2D	$-CH_3$	I	toluene, 53/72	2:1::1-butanol:DMF, 75	74	271-273	48.75/48.81	3.84/3.98	I, 32.19/31.95
2E	$-CH_3$	BF_4	[l]	not needed	89	278-280	54.27/54.18	4.27/4.55	F, 21.46/19.70
2F	$-CH_3$	ClO_4	[m]	not needed	100	288-290	52.54/52.43	4.13/4.30	Cl, 9.42/9.24
2G	$-(CH_2)_2Br$	Br	$Br(CH_2)_2Br$, 12/19 [j]	not needed	85	252-253 dec	46.39/46.87	3.66/3.63	–
2H		$-(CH_2)_2SO_3$	see text	water, 200	92	331-332	56.66/56.67	4.48/4.78	S, 8.90/9.19
2I		$-(CH_2)_3SO_3 \cdot 1/2\ H_2O$	toluene, 50/72	water, 90	86	324-325	56.39/56.22 [n]	5.00/5.37 [n]	–
2J		$-(CH_2)_4SO_3 \cdot 1/2\ H_2O$	toluene, 50/22	water, 125	61	297-298	57.42/57.36 [k]	5.33/5.47 [k]	–
2K	$-(CH_2)_5Br$	Br	$Br(CH_2)_5Br$, 16/18 [o]	not needed	98	155-170 dec	49.82/50.74	4.60/4.77	–
2L		$-(CH_2)_5SO_3 \cdot 1/2\ H_2O$	see text	water, 90	94	295-297	58.37/58.09	5.63/5.64	S, 7.79/7.10
2M	$-CH_2C_6H_5 \cdot Cl(CH_2)_2Cl$	Cl	$Cl(CH_2)_2Cl$,-/24	$Cl(CH_2)_2Cl$	≈ 30	214-216 [p]	–	–	–
2N	$-CH_2C_6H_4CN \cdot 3H_2O$	Br	$Cl(CH_2)_2Cl$,-/24	95% ethanol, 110	≈ 30	260-262	54.99/55.23	4.82/4.94	N, 8.36/8.28
2O	$-CH_2C_6H_4CH{=}CHC_6H_5 \cdot 3H_2O$	Cl	$Cl(CH_2)_2Cl$,-/24	2-propanol	33	235-237	70.93/70.76	5.56/5.36	Cl, 6.98/6.85 [q]
2P	$-CH_2CH{=}CH_2$	ClO_4 [r]	$Cl(CH_2)_2Cl$,-/24	water	–	227-229 dec	55.04/54.90	4.36/4.46	N, 7.13/7.07
3A	$-CH_3$	Ms	$Cl(CH_2)_2Cl$,-/6	2-propanol	75	218-219.5	59.39/59.40	5.98/6.18	N, 6.93/6.83
3B		$-(CH_2)_3SO_3 \cdot H_2O$	$Cl(CH_2)_2Cl$,-/8	95% ethanol	52	275-276	55.74/56.35	6.19/6.24	N,6.19/6.14
4A	$-CH_3$	Ts	acetonitrile,-/7	2-propanol	84	229.5-231.5	61.96/61.86	4.49/4.58	N, 6.57/6.51
4B	$-CH_2C_6H_4CH{=}CHC_6H_5 \cdot 1.5H_2O$	Cl	$Cl(CH_2)_2Cl$,-/24	2-propanol	30	245-246.5	70.22/70.41	5.08/4.77	N, 5.65/5.64
5A	$-CH_3$	Ts	$Cl(CH_2)_2Cl$, 7/8	3:1::$Cl(CH_2)_2Cl$:acetonitrile	71	189-190	65.38/65.34	5.25/5.40	N, 6.63/6.49
5B	$-CH_3$	ClO_4	[s]	95% ethanol	64	273-275 dec	54.79/54.74	4.31/4.44	N, 7.99/7.89
5C		$-(CH_2)_3SO_3 \cdot H_2O$	$Cl(CH_2)_2Cl$,-/7.5	82% ethanol	65	311-313 dec	57.43/57.82	5.38/5.33	N, 7.44/7.39
6A	$-CH_3 \cdot 1/2\ Cl(CH_2)_2Cl$	Ts	$Cl(CH_2)_2Cl$,-/7.5	$Cl(CH_2)_2Cl$, 2X	81	208-209 [t]	58.33/59.22	4.73/4.92	N, 5.72/5.35
6B	$-CH_3$	ClO_4	[u]	water	–	252-255 dec	52.11/52.25	3.83/3.88	N, 7.60/7.19

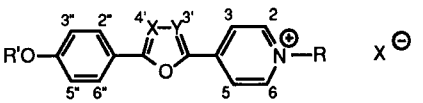
Table 3 (continued)

No. [a]	R	An	Rxn Solv, Vol [b] /Time	Recryst Solv [c]	Yield	MP	Elemental Assay: Calculated/Found % C	% H	% Other
7A	$-CH_3$	ClO_4	[v]	methanol, 125	40	260-261.5	61.09/61.05	4.15/4.33	N, 6.79/6.77
8A	$-CH_3$	ClO_4	[v]	methanol	24	224-226.5	61.90/61.17	4.49/4.59	N, 6.56/6.52
9A	$-CH_3$	Ts	toluene, 30/7.5	2-propanol	–	230-231.5	59.66/59.67	4.32/4.41	Cl, 8.00/8.21 [w]
10A	$-(CH_2)_{11}CH_3$	Ts	toluene, 20/32	dibutyl ether, 25	83	144.5-146	72.41/72.02	8.41/8.47	N, 4.33/4.12 [x]
11A	$-CH_3$	Ms	toluene, 60/16	1-butanol:DMA, 3X	39	256-262	63.00/62.14	5.06/5.16	N, 6.39/6.33 [y]
11B		$-(CH_2)_4SO_3$	toluene, 60/96	not needed	82	328-331 dec	64.64/64.62	5.21/5.13	S, 6.90/6.87 [z]
12A	$-CH_3$	Ms	acetonitrile, 20/24	[aa]	100	255-256.5	58.75/58.59	5.19/4.52	S, 8.25/8.42
13A	$-CH_3$	Ms	acetonitrile, 22/24	[aa]; aq 1-propanol	57	278-282	57.74/56.75	4.85/5.19	S, 8.56/8.73
14A	$-CH_3$	Ms	toluene, 15/4	2-propanol, 2X	86	221-222.5 dec	56.34/56.46	5.01/5.08	N, 7.73/7.64
15A	$-CH_3$	Ms	toluene, 20/4	2-propanol	38	238-240 dec	52.88/53.06	4.72/4.73	N, 11.56/11.33
16A	$-CH_3 \cdot 1/2H_2O$	Ms	toluene, 33/20	2-propanol	95	156-159 dec	58.36/58.38	5.44/5.42	N, 3.78/3.74
17A	$-CH_3 \cdot 2H_2O$	Ts	$Cl(CH_2)_2Cl$, 20/18	2-propanol	91	182-183.5	66.34/66.03	5.10/5.22	S, 7.38/7.42 [bb]
18A	$-CH_3 \cdot 2H_2O$	Ts	$Cl(CH_2)_2Cl$, 22/18	2-propanol	63	210-212	62.22/62.25	5.43/5.27	S, 6.64/6.93 [cc]
19A	$-CH_3$	Ts	$Cl(CH_2)_2Cl$,-/22	2-propanol	93	229-230	63.70/63.68	4.68/4.81	F, 4.20/4.32 [dd]
19B	$-CH_3$	ClO_4	$Cl(CH_2)_2Cl$,-/22	50% methanol, 2X	–	315-320 dec	53.62/53.60 [k]	3.71/3.52 [k]	F, 4.99/5.13 [ee]
20A	$-CH_3$	Ts	$Cl(CH_2)_2Cl$,16/24	methanol	98	298.5-301.5	69.69/68.34	4.60/4.52	S, 6.18/5.96 [ff]
22A	$-CH_3$	Ts	$Cl(CH_2)_2Cl$,15/22 [gg]	2-propanol, 250	76	243-244 dec	65.70/65.08	4.79/4.67	S, 7.62/7.35 [hh]
23A	$-CH_3$	Ts	$Cl(CH_2)_2Cl$,27/24 [gg]	2-propanol, 220	76	254-255 dec	63.99/64.18	4.92/4.84	S, 7.12/7.03 [ii]
24A	$-CH_3 \cdot H_2O$	Ts	$Cl(CH_2)_2Cl$,40/24 [gg]	2-propanol	84	217-219	64.35/65.48	5.62/5.38	S, 6.87/6.51 [jj]
25A	$-CH_3 \cdot Cl(CH_2)_2Cl$	Ts	$Cl(CH_2)_2Cl$,40/22 [gg]	2-propanol, 15	70	205-207 dec	58.22/57.68	5.24/5.48	S, 5.55/5.70 [kk]

[a] Numerals refer to the free bases in Tables 1 and 2. [b] Milliliters per gram of base. [c] Milliliters per gram of salt. [d] All C_6H_4 groups are 1,4-phenylene *(para)*. [e] Hours at reflux. [f] From treatment of **1C** as in [r]. [g] *(E)*. [h] Ts = tosylate = p-toluenesulfonate. [i] Ms = mesylate = methanesulfonate. [j] Reaction temperature was 72°. [k] Mean of duplicate assays. [l] An aqueous solution of **2A** was treated with a 10% excess of 60% tetrafluoroboric acid. [m] An aqueous solution of **2A** was treated with a 10% excess of 61% perchloric acid. [n] Mean of triplicate assays. [o] Reaction temperature was 80°. [p] When plunged into a bath at 105° melted, desolvated, resolidified, and remelted as above. PMR indicated presence of 1 mole of 1,2-dichloroethane. [q] N, 5.52/5.48. [r] The quaternary with allyl bromide was treated with perchloric acid in 50% methanol. [s] From treatment of **4A** as in [r]. [t] Desolvates at 160-170°. [u] From treatment of **6A** as in [r]. [v] From treatment of the tosylate as in [r]. [w] N, 6.33/6.21. [x] S, 4.96/5.35. [y] S, 7.31/7.56. [z] N, 6.03/5.92. [aa] Diluted at bp with an equal volume of toluene and cooled to 25°. [bb] N, 6.45/6.31. [cc] N, 5.81/5.69. [dd] N, 6.19/6.45; S, 7.08/6.98. [ee] N, 7.36/7.28. [ff] N, 5.40/5.61. [gg] Ether added in 1-5 volumes to precipitate salt. [hh] N, 6.66/6.61. [ii] N, 6.21/6.17. [jj] N, 6.01/6.04. [kk] N, 4.85/5.02.

Table 4

Proton Chemical Shifts (δ downfield in ppm from internal TMS) of Selected Quaternary Salts at 5–10% in Trifluoroacetic Acid on Varian T–60



No.	2– and 6–H	3– and 5–H	3'–H	4'–H	2"– and 6"–H	3"– and 5"–H	Hs in R	Hs in R'	Hs in X	Other Hs
2A	8.98, d, J = 6 Hz	8.75, d, J = 6 Hz	–	7.96, s	7.87, d, J = 9 Hz	7.18, d, J = 9 Hz	4.61, s, CH_3	4.08, s, CH_3	2.45, s, $ArCH_3$ 7.31, d, J = 8 Hz, Hs *o* to ArS 7.80, d, J = 8 Hz, Hs *m* to ArS	–
2B	8.95, d, J = 6 Hz	8.73, d, J = 6 Hz	–	7.98, s	7.90, d, J = 9 Hz	7.20, d, J = 9 Hz	4.60, s, CH_3	4.05, s, CH_3	3.16, s, CH_3SO_3	–
2C	8.96, d, J = 6 Hz	8.73, d, J = 6 Hz	–	8.00, s	7.90, d, J = 9 Hz	7.18, d, J = 9 Hz	4.61, s, CH_3	4.06, s, CH_3	–	–
2E	9.08, d, J = 6 Hz	8.81, d, J = 6 Hz	–	8.07, s	7.98, d, J = 9 Hz	7.30, d, J = 9 Hz	4.66, s, CH_3	4.13, s, CH_3	–	–
2F	8.93, d, J = 6 Hz	8.70, d, J = 6 Hz	–	7.96, s	7.87, d, J = 9 Hz	7.17, d, J = 9 Hz	4.56, s, CH_3	4.02, s, CH_3	–	–
2I	9.1, d, J = 6 Hz	8.71, d, J = 6 Hz	–	7.98, s	7.88, d, J = 9 Hz	7.25, d, J = 9 Hz	5.08, t, J = 7 Hz, NCH_2 3.50, t, J = 7 Hz, CH_2S 2.90, m, CCH_2C	4.07, s, CH_3	–	–
2J	9.00, d, J = 6 Hz	8.66, d, J = 6 Hz	–	7.93, s	7.85, d, J = 9 Hz	7.20, d, J = 9 Hz	4.85, br t, NCH_2 3.40, t, J = 7 Hz, CH_2S 2.30, m, CCH_2CH_2C	4.06, s, CH_3	–	–
2L	9.11, d, J = 6 Hz	8.82, d, J = 6 Hz	–	8.07, s	7.98, d, J = 9 Hz	7.30, d, J = 9 Hz	4.85, br t, NCH_2 3.43, br t, CH_2S 2.20, br m, $C(CH_2)_3C$	4.15, s, CH_3	–	–
10A [a]	9.30, m	8.30, m	–	8.30, m	–	7.14, m	4.84, br, NCH_2 2.20, br s, $C(CH_2)_{10}C$ 0.87, br t, J ≈ 5 Hz, CCH_3	–	2.22, s, $ArCH_3$ 7.30, d, J ≈ 8 Hz, Hs *o* to ArS 7.70, m, Hs *m* to ArS	1.32, s, t–Bu 2.27, s, 2",6"-CH_3

Table 4 (continued)

No.	2– and 6–H	3– and 5–H	3'–H	4'–H	2''– and 6''–H	3''– and 5''–H	Hs in R	Hs in R'	Hs in X	Other Hs
12A	9.05, d, J = 6 Hz	8.82, d, J = 6 Hz	–	8.06, s	7.73, br s	7.13, d, J = 9 Hz, 5''H	4.66, s, CH_3	4.50, t, J = 6 Hz, $ArCH_2CH_2CH_2O$ 3.04, t, J = 6 Hz, $ArCH_2CH_2CH_2O$ 2.25, m, $ArCH_2CH_2CH_2O$	3.20, s, CH_3SO_3	–
14A [b]	9.08, d, J = 7 Hz	8.30, d, J = 7 Hz	8.30, s	–	8.11, d, J = 9 Hz	7.05, d, J = 9 Hz	4.45, s, CH_3	3.91, s, CH_3	3.16, s, CH_3SO_3	–
15A [b]	9.42, d, J = 6 Hz	8.69, d, J = 6 Hz	–	–	8.14, d, J = 8 Hz	7.11, d, J = 8 Hz	4.60, s, CH_3	3.91, s, CH_3	3.08, s, CH_3SO_3	–
16A [c]	9.81, d, J = 6Hz	8.32, d, J = 6Hz	8.00, d, J = 5Hz	7.24, d, J = 5Hz	8.00, d, J = 8Hz	7.09, d, J = 8Hz	4.44, s, CH_3	3.87, s, CH_3	2.38, s, CH_3SO_3	–

[a] Run by M. A. Aziz on Bruker NR-80 in deuteriochloroform. [b] Bruker NR-80 in Unisol™. [c] Varian EM360L in DMSO-d_6.

Table 5

Interpretation of ^1H NMR (Varian VXR 300 MHz) Spectrum of 2-(4-Pyridyl)phenanthreno[9,10-*d*]-1,3-oxazole (**20**)

H assignments	δ (ppm)	# of Hs	Multiplicity	J (Hz)
H_a	8.84	2H	dd	1.5, 4.5
H_b	8.20	2H	dd	1.5, 4.5
H_d, H_f, H_g, H_i	7.71-7.77	4H	m	
H_h, H_e	8.72-8.77	2H	m	
H_c	8.62	1H	dd	2.0, 7.4
H_j	8.35	1H	dd	2.1, 7.2

Table 6

Interpretation of ^{13}C NMR (Varian VXR 300 MHz) Spectrum of 2-(4-Pyridyl)phenanthreno[9,10-*d*]-1,3-oxazole (**20**)

Carbons	δ (ppm)
C-1	150.70
C-2	120.57
C-3	134.50
C-4	159.61
C-5	135.63
C-6	145.56
C-7	125.93
C-8	122.94
C-10	123.85
C-12	129.87
C-13	129.08
C-15	123.50
C-17	121.11
C-18	120.77
C-9, C-11, C-14, C-16	126.61, 127.13, 127.49, 127.69

means of potassium hydroxide, and the resulting phthalamic acid was fully hydrolyzed with hydrobromic acid.

Oxazole **11** was prepared uniquely by a palladium-catalyzed coupling of the Grignard Reagent from 4-bromoanisole with 5-(4-bromophenyl)-2-(4-pyridyl)oxazole, itself prepared by the method used for oxazole

3. The 200 MHz ^{1}H nmr spectrum in the Experimental section was in excellent agreement with the proposed structure, and the sulfobutyl zwitterion **11B**, which may be considered a derivative of oxazole **11**, had assays for 4 elements in excellent agreement with theory.

Toward oxazole **12** the simple chroman required was not commercially available. A short reported synthesis of chroman from the aluminum chloride catalyzed cleavage of 1,3-diphenoxypropane [15] was improved by substitution of 1-bromo-3-chloropropane for the costly 1,3-dibromopropane, and dimethylformamide for acetone [16] in the preparation of 1,3-diphenoxypropane. The cleavage of this ether was not complete; some diether and other impurities were present in the chroman prepared by this method, as shown by gas chromatography, and could not be removed by careful fractional distillation. An older route to chroman [17] was modified by use of sodium bis(methoxyethoxy)aluminum hydride instead of lithium aluminum hydride to reduce 3,4-dihydrocoumarin to the diol in 92% yield. Cyclization with phosphoric acid gave 82-84% yields of pure chroman. Friedel-Crafts acylation of the chroman with bromoacetyl chloride gave a 100% yield of the crude liquid phenacyl bromide, which was subjected to the Delépine reaction, *etc.*, analogously to Figure 3. Oxazole **13** was prepared in a similar manner from the commercially available 2,3-dihydrofuran.

Synthesis of the "reverse" oxazole **14** (Figure 4) took advantage of the preparation of 2,2-diethoxy-2-(4-pyridyl)ethylamine **37** in Organic Syntheses [18]. This diamine condensed with 4-methoxybenzoyl chloride **36** to form an amide **38**. Deprotection of the ketone to give **14**-amide was accomplished with 1 *M* hydrochloric acid, followed by cyclodehydration to oxazole **14**.

The related oxadiazole **15** (Figure 5) was obtained by standard methods. In this case, the preferred cyclodehydration reagent was thionyl chloride.

The related furan **16** (Figure 6) was not prepared by the conventional cyclodehydration of a 1,4-diketone, but instead by successive palladium–catalyzed aryl couplings. The key intermediate **41** could not be prepared by the reported Gomberg coupling reaction [19]; no more than 1% yield was achieved despite repetition. The direct lithiation of furan with butyllithium leading to 2-arylfurans [20] was modified successfully as follows: Furan (**40**) reacted with *t*-butyllithium to form 2-furyllithium (**40a**). Reaction with anhydrous zinc chloride gave 2-furylzinc chloride (**40b**). Without isolation, the zinc compound was coupled with 4-bromoanisole to give **41** in 77% yield, mp 53.5-55°. An unusual bp was observed, possibly due to a Diels-Alder reaction and its reversal. A second lithiation gave **41a** which was converted to the zinc derivative **41b**. Free 4-chloropyridine **42a** was prepared from its hydrochloride **42** under anhydrous conditions by use of methylmagnesium chloride as a base. A second palladium catalyzed coupling with **41** gave the furan **16** in 64% yield.

An attempt was made to prepare oxazole **56** (in Figure 10 only). The conventional route [21] shown gave **56**-amide, which was well-characterized. Use of the cyclodehydration reagent thionyl chloride gave no isolable oxazole; a small amount of 2,5-bis(4-methoxyphenyl)piperazine **57** was isolated; this was identified by ^{1}H nmr and reported mp [22]. (Note the isolation of a small amount of the analogous 2,5-bis(fluorophenyl)piperazine in the preparation of oxazole **4**). No other cyclodehydration reagents were tried.

Syntheses of 2-(4-Pyridyl)cycloalkano[*d*]oxazoles.

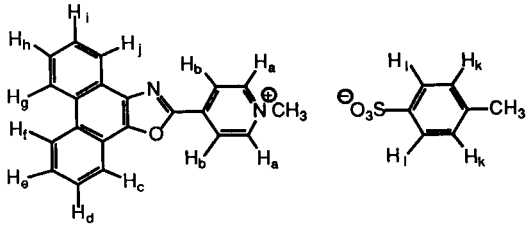
All the oxazoles in Table 2 were prepared by the sequence shown in Figure 7. The aminoketones **46a-c** were accompanied by the aminonaphthols **45a-c**. These must be removed by repeated recrystallization or the subsequent products become contaminated with green or black dyes produced by air oxidation of the aminonaphthols. Oxazoles **17-18** and their salts **17A-18A** have been registered with the U. S. Patent Office as laser dyes [23].

In the preparation of oxazoles **20-21** the hydrogenations of the quinone monoximes (example **50** in Figure 8) were stopped promptly when the theoretical amount of hydrogen was taken up to avoid formation of reactive aromatic amines. Conversion of the α-aminoketone from phenanthrenequinone monoxime to its isonicotinamide gave a low yield of difficult-to-purify material which was not converted to oxazole **20** with phosphorus oxychloride. The one-step method of Afanasiadi succeeded to give oxazole **20** in 35% yield. Its ^{1}H and ^{13}C nmr spectra (Tables 5 and 6) support the proposed structure. Some ^{13}C chemical shifts for oxazoles have been reported [24].

Oxazole **21** was not isolated from either the one-step or two-step variants of the synthetic scheme in Figure 8; instead a yellow solid displaying a blue fluorescence in dimethylsulfoxide was obtained, whose elemental assays and ^{1}H nmr spectrum (Table 8) indicated that the structure was the Diels-Alder adduct **51**. A ^{13}C nmr spectrum was not possible due to insolubility. This compound could have been formed by dimerization of oxazole **21** followed by elimination of water and the isonicotinamide group, or by thermochemical cycloaddition of oxazole **21** to **21**-amide followed by the same elimination. There are

Table 7

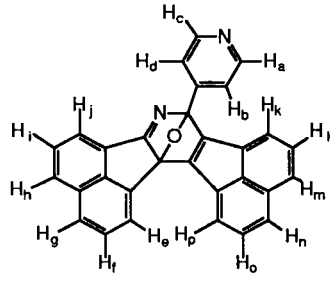
Interpretation of ^{1}H NMR (Varian VXR 500 MHz) Spectrum of 2-(4-Pyridyl)phenanthreno[9,10-*d*]-1,3-oxazole *p*-Toluenesulfonate (**20A**)



H assignments	δ (ppm)	# of Hs	Multiplicity	J (Hz)
Methyl of Ts.	2.26	3H	s	
N-methyl	4.42	3H	s	
H_a	9.16	2H	d	6.9
H_b	8.84	2H	d	6.9
H_d, H_f, H_g, H_i	7.81-7.93	4H	m	
H_h, H_e	8.96-9.03	2H	m	
H_c, H_j	8.47-8.54	2H	m	
H_k	7.47	2H	dd	2.1, 7.5
H_l	7.10	2H	d	7.8

Table 8

Interpretation of ^{1}H NMR (Varian VXR 500 MHz) Spectrum of Postulated Diels-Alder Adduct **51**



δ (ppm)	# of Hs	Multiplicity	J (Hz)	Hs
7.45	1H	t	8.25	H_f, H_i, H_l, H_o
7.49	1H	t	7.50	
7.77	1H	dd	7.0, 8.0	
8.06	1H	t	7.5	
7.82-7.90	5H	m		H_e, H_g, H_h, H_j, H_k, H_m, H_n, H_p
8.02	1H	d	8.0	
8.03	1H	d	8.0	
8.38	1H	d	6.5	
8.67	1H	d	7.0	H_a, H_b, H_c, H_d
8.78	1H	d	7.0	
8.88	2H	bd	5.0	

several reports of Diels-Alder reactions in which 1,3-oxazoles act as dienes [25a-c].

Oxazoles **22-25** were prepared in poor yields by the method exemplified in Figure 7 utilizing the one-step process. In the synthesis of oxazole **23** its isonicotinamide was isolated as a by-product. The identities of oxazoles **23-25** were confirmed by elemental assays, and for all them by formation of the quaternary salts **22A-25A** which also were assayed.

Syntheses of Quaternary Salts.

Usually the appropriate electrophilic quaternizing agent was heated with the 2-(4-pyridyl)oxazole as shown in Figures 2-4. Since many 2,5-diaryl-1,3-oxazoles have been quaternized on the oxazole nitrogen, there exists the possibility that quaternization could have occurred other than on the pyridine nitrogen. This was considered in the quaternization of oxazole **1** and its 2- and 3-pyridyl isomers by Ott *et al.* [1] who found that only mono- tosylates were formed even with excess methyl tosylate. Quaternary salts **1B-1C**, **1E-2D**, **2G**, **2I-2K**, **2M-5A**, **5C-6A**, and **9A-25A** were prepared in this manner (Table 3). Formation of solvates was frequent, but not consistent. The most common solvent for quaternization, acetonitrile, was found less useful overall than toluene and 1,2-dichloroethane from which the salts would precipitate quantitatively.

The relatively insoluble perchlorates **1D**, **2F**, **5B**, **6B-8A** and the tetrafluoroborate **2E** were obtained by action of the acid on a solution of the tosylate.

The sulfo zwitterions **2H** and **2L** were formed by reaction of sodium sulfite with the appropriate bromoalkyl quaternary salt following the example of Barnhurst [26].

Elemental assays are given in Table 3 and ^{1}H nmr interpretations in Tables 4 and 7.

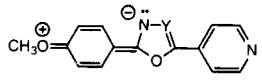
Photophysical Properties of 5-Aryl-2-(4-pyridyl)oxazoles and Related Compounds.

Afanasiadi [12] has determined the absorption and fluorescence spectra of a number of the free bases. We find that for the one base in common, oxazole **2**, our absorption maximum of 333 nm may be reconciled with Afanasiadi's 338 nm, and our fluorescence maximum of 382 nm *vs.* Afanasiadi's 440 nm by the difference in solvent: cyclohexane in our case *vs.* ethanol. Similarly extreme positive solvatofluorochromism has been reported for 2-[4-(difluoromethylsulfonyl)phenyl]oxazoles [27].

We supposed that the related oxazole **14** would have similar properties; instead both wavelengths were hypsochromically shifted, and the extinction coefficient was much higher. In the related oxadiazole **15** these wavelengths are further hypsochromically shifted. In the related furan **16** there is little difference in wavelengths from those of oxazole **2**, but the extinction

coefficient was much higher. We noticed that the melting points of **14** (174°) and **15** (195°) are significantly higher than those of oxazole **2** (115°) or furan **16** (150°). This is consistent with a substantial contribution in the ground state of the resonance form shown in Figure 11 for oxazole **14** and oxadiazole **15** which is likely to be a far smaller contributor to the ground states of oxazole **2** or furan **16**. This form would enhance coplanarity between the phenyl and middle rings as shown, making the molecules as a whole more rigid.

Fig. 11. Resonance Form of Ground States of Oxazole 14 and Oxadiazole 15



14, Y = CH
15, Y = N

A 4-methyl group on oxazole **6** produced moderate bathochromic shifts compared with oxazole **4**; this was carried over into the perchlorate salts (Table 1).

As both the solubility, fluorescence, and lasing properties of the quaternary salts had been of greatest interest, these properties of the free bases received less attention.

Photophysical Properties of Quaternary Salts.

The absorption (without extinction coefficients) and fluorescence peaks of most of the salts in Table 3 have been reported, along with their performance as flash-lamp pumped laser dyes [3,28,29] and with a number of fluorescence quantum yields [29]. The most effective laser dye was zwitterion **2I** in ethanol-water [29]. The major resonance form of the S_1 state of these salts has been proposed [28].

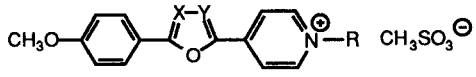
The toluene-soluble salt **10A** (abs. max 347 nm, ε = 19,000, fl. max 510 nm in 95% ethanol; 346 nm, ε = 16,000, fl. max ≈490 nm in toluene) was not effective in poly(methyl methacrylate) as a laser dye. It was too photochemically unstable to be used as a wave-shifter in a luminescent solar concentrator design for photovoltaic power generation. It was too insoluble to serve as a wave-shifter in polysiloxane for scintillation counting.

The salts **11A** (abs. max 362 nm, ε = 28,000 in ethanol) and the zwitterion **11B** (abs. max 410 nm, ε = 25,000 in ethanol) both displayed a weak blue fluorescence. The additional benzene ring actually diminished the facility of charge transfer in the S_1 state towards the positively charged nitrogen atom. Afanasiadi found similar results for the demethoxy free base **11** and its tosylate quaternary salt [12]. Similar hypsochromic shifts have been observed when biphenyl or terphenyl is substituted for phenyl in dioxazoles [30]. Zwitterion **11B** lased poorly when tested at Avco-Everett Research Laboratories.

Electronic spectral data for salts **14A-16A** are reported now in Table 9; **2A** is included for comparison. Salt **14A** displayed a small Stokes' shift, a high extinction coefficient, and a powerful fluorescence compared with salt **2B**. Quaternary salts of **2** and **14** are under active investigation as photostable and water-soluble fluorescent dyes for biological staining.

Table 9

Photophysical Properties of Selected Quaternary Salts



No.	X	Y	λ max abs [a]	ε x 10^{-3}	λ max Fl Em [a]	SS	Φ in EtOH [b]	Φ in EtOH-Water [c]
2B	CH	N	260 nm	14.8	540 nm	135 nm	0.92	0.77
			405	20.4				
14A	N	CH	253	13.4	495	118	0.62	0.63
			268	13.4				
			377	30.5				
15A	N	N	261	20.5	540	186	0.09	0.01
			354	17.8				
16A	CH	CH	262	15.0	515	93	0.05	0.05
			272	13.5				
			422	36.6				

[a] In ethanol. See [b-d] in Table 1. [b] The fluorescence quantum yield, Φ, was determined by the dilute solution method using a Farrand Spectrofluorometer Mk. I rebuilt to produce corrected spectra to 750 nm by Optical Technology Devices, Elmsford, NY, with **2A** as a reference standard, reported, Φ = 0.73 as "Ox 2" in [29]. [c] 1:1 by volume.

Experimental

General.

All melting points were determined in unsealed capillary tubes with 76 mm immersion thermometers and needed no correction. Those below 280° were obtained in a heated oil bath (Thomas-Hoover Unimelt, Arthur H. Thomas Co.). Those above 280° were obtained in a heated aluminum block (Mel-Temp, Laboratory Devices Co.). Infrared spectra were determined in potassium bromide pellets (unless otherwise noted) with a Beckman IR-4230, a Perkin-Elmer 297, or a Perkin-Elmer 1600 series FTIR using a diffuse reflectance cell. Abbreviations: m = medium intensity (ir) or multiplet (pmr), sh = shoulder, st = strong, v = very, br = broad. Proton magnetic resonance (pmr) spectra were obtained with a Varian T-60 spectrometer (unless otherwise specified) using 5-10% solutions in trifluoroacetic acid, unless deuterochloroform is specified, always with tetramethylsilane as an internal standard. Chromatographic purification by extraction from an "Ace-Kau" means that boiling solvent was allowed to fall on a solid sample and pass through adsorbent in a special apparatus [31], (Ace-Kauffman Column, Ace Glass Co). Most solids were dried in a vacuum oven with a water aspirator at 30 torr. Most stirring in round-bottomed flasks was accomplished with teflon-coated magnets of prolate spheroid shape driven by a Corning PC-133 unit. Standard taper joints were often fitted with teflon sleeves, but never greased except for distillations under vacuum. Evaporations were usually carried out with a rotary evaporator under a final pressure of 30 torr. Elemental analyses were carried out by Microanalysis, Inc., Wilmington, DE; Oneida, Rensselaer, NY; Galbraith, Knoxville, TN, or Desert Analytics, Tucson, AZ. Thin-layer chromatography (tlc) was carried out with Whatman MK6F silica 1 x 3 inch plates visualized with short- and long-wave ultraviolet light unless otherwise specified. The decolorizing carbon used was Norit, neutral (Fisher C-170).

5-Aryl-2-(4-pyridyl)oxazoles and Related Compounds

Sodium Salt of 2-Isonitroso-4'-methoxyacetophenone.

A 1-liter 3-necked flask was equipped with a nitrogen inlet, thermometer, magnetic stirrer, reflux condenser, and powder addition funnel. To the flask was added 400 ml of *t*-butyl alcohol, then sodium hydride (8.80 g of 60% dispersion in oil, 5.28 g on 100% basis, 0.220 mole, Aldrich 19,923-0) in portions during 10 minutes. An exotherm from 22° to 37° was observed. Then 4'-methoxyacetophenone (**1**, 30.0g, 0.200 mole, Aldrich 11,737-4) was added rapidly, causing an endotherm to 30°, and resulting in a clear solution. The powder addition funnel was replaced with a liquid addition funnel containing isoamyl nitrite (28.1 g, 0.240 mole, Eastman P436), which was added dropwise during 10 minutes. A brick-red solid formed slowly, and the suspension was stirred for 1 hour and filtered. The red solid was slurried with 100 ml of acetone for 10 minutes, refiltered, and dried at 50°/30 torr/18 hours to give 14.6g (36%). Attempted determination of melting point resulted in a color change from red to buff at 170° and no further change up to 275°. The solid was insoluble in acetone and very soluble in water.

A later batch was obtained in 57% yield; ir: v 3430 (br w), 2930 (w), 2830 (w), 1595, 1560 (s), 1540, 1435, 1250, 1183, 1162, 1100, 1040 (s), 1026, 885, 838, 780, 755, 690, 613.

Its identity was confirmed by conversion to 4'-methoxyphenacylammonium chloride by Method A below.

4'-Methoxyphenacylammonium Chloride.

Method A: Reduction of Isonitroso Group.

The sodium salt of 2-isonitroso-4'-methoxyacetophenone (**2**, 14.7 g, 0.073 mole) and the 10% palladium on carbon catalyst (0.5 g, Alfa 89109) were placed in a 400 ml Parr bottle. A cold mixture of 130 ml of methanol, 65 g of ice, and 20 ml of 12 *M* hydrochloric acid was added, and hydrogenation begun. No uptake was observed. The mixture was filtered with suction, and the solid washed with 100 ml of methanol, dissolving most of it. New catalyst (0.5 g) was placed in 20 ml of methanol in the Parr bottle, the yellow filtrate added, and hydrogenation was begun again, resulting in 19.6 lbs of uptake in 2 hours. The mixture was filtered, and the almost colorless filtrate (pH ≈ 0.5) was evaporated almost to dryness, treated with 100 ml of absolute ethanol, evaporated to dryness, and the tan solid was recrystallized from 150 ml of 2-propanol at 2° to obtain pale yellow crystals, 6.40 g (44%), mp 200-202°dec, which were very soluble in water, but did not appear to be hygroscopic. The analytical sample was recrystallized from 25 ml/g of 1-butanol, mp 205-206.5°, no dec.

Anal. Calcd. for $C_9H_{12}ClNO_2$: N, 6.98; Cl, 17.17. Found: N, 6.36; Cl, 16.90.

The product of a later run, mp 201.5-202.5°, was obtained in 42% yield; pmr: δ 4.07 (s, 3H, OCH_3), 4.93 (br q, 2H, $COCH_2$), 7.21 (d, J = 8Hz, 2H, Hs *ortho* to OCH_3), 7.6 (br, 3H, $^+NH_3$), 8.12 ppm (d, J = 8Hz, 2H, Hs *ortho* to C=O).

The product of a still later run, mp 198-200°, was obtained in 30% yield; ir: v 3400 (br), 2920 (br), 2610 (w), 1672, 1600, 1498, 1465, 1425, 1383, 1320, 1265, 1252, 1177, 1020, 832.

Method B: By the Delépine Reaction (Figure 3).

Hexamethylenetetramine (**31**, 15.9 g, 0.114 mole) was dissolved in 600 ml of chloroform with stirring; 4'-methoxyphenacyl bromide (**30**, 25.2 g, 0.111 mole) was then added, and the stirring was continued overnight at room temperature. The precipitated salt **32** was filtered, washed twice with chloroform and dried to obtain 38.3 g (93%). All of this salt was stirred in 250 ml of methanol, cooled in an ice-water bath, and treated with 40 ml (0.49 mole) of 12 *M* hydrochloric acid. The mixture was allowed to stand at room temperature for 3 days. Complete solution was observed after 5 hours; new solid (ammonium salts) began to precipitate soon thereafter. The solid was filtered off and washed twice with

10 ml of cold methanol. After the combined filtrates had been evaporated to dryness, the residue was extracted with one 400 ml and one 50 ml portion of boiling absolute ethanol. The extracts were cooled at 5°, filtered; and the solid was washed with ethanol-ether, then with ether, and dried to yield 16.5 g (73%) of product, mp 187-188°dec. Adding a large excess of ether to the ethanolic liquor gave 5.6 g of less pure salt.

4'-Methoxyphenacylammonium Bromide (**33**) by Delépine Reaction.

In a 1-liter tall beaker with magnetic stirring hexamethylenetetramine (**31**, 30.8 g, 0.220 mole, MC&B) was dissolved in 400 ml of chloroform. To the clear solution was added 4'-methoxyphenacyl bromide (**30**, 51.8 g, 0.226 mole, Aldrich 11,566-5), causing formation of a heavy precipitate in seconds, which was stirred overnight. After addition of 200 ml of *t*-butyl methyl ether the solid was filtered, washed with 200 ml of *t*-butyl methyl ether, dried at 70°/30 torr/6 hours; yield 80.8 g (98%) of the quaternary salt **32**.

The salt **32** was transferred to a 2-liter round flask, and 550 ml of methanol and 75 ml of 48% hydrobromic acid (Joel Freeman Co.) were added. The mixture was magnetically stirred for 3 days. The resulting clear amber solution was evaporated to ≈ 250 ml with the bath temperature ≤35°. The suspension was transferred to a 400 ml beaker with the aid of a few ml of 48% hydrobromic acid, kept at -22°, filtered on medium sintered glass, pressed well, washed with a solution of 25 g of sodium bromide in 25 ml of water, and dried at 20°/0.1 torr/26 hours to give 94 g of pale solid. This was recyrstallized from 800 ml of 1-butanol at 0°, filtered, washed with 100 ml of *t*-butyl methyl ether, and dried at 70°/30 torr/3 days to give well-defined tan prisms, mp 200-203°dec, 35.1 g (65% from **30**); ir: 2950 (vbr), 2665 (w), 2605 (w), 1910, 1678, 1600, 1495, 1462, 1431, 1383, 1314, 1260, 1178, 1124, 1018, 970, 831, 812, 635; pmr: δ 4.03 (s, 3H, OCH_3), 4.90 (q, J = 5Hz, 2H, $COCH_2$), 7.10 (d, J = 8Hz, 2H, Hs *ortho* to OCH_3), 7.45 (br, 3H, $^+NH_3$), 8.05 ppm (d, J = 8Hz, 2H, Hs *ortho* to C=O).

The analytical sample was obtained by recrystallization from 10 ml/g of 1-butanol at 0°, mp 204-5°, no dec.

Anal. Calcd. for $C_9H_{12}BrNO_2$: N, 5.64; Br, 32.47. Found: N, 5.61; Br, 32.42.

N-(4'-Methoxyphenacyl)isonicotinamide (**2**-Amide).

Method A: From the Phenacylammonium Chloride.

A 100 ml round flask equipped with magnetic stirring, a thermometer, and a 15 cm high chimney bearing a powder funnel, was charged with isonicotinoyl chloride hydrochloride (**34**, 6.41 g, 0.036 mole, Aldrich 22,875-3), then 4'-methoxyphenacylammonium chloride (6.05 g, 0.030 mole), and finally with 60 ml of pyridine previously dried over 4A molecular Sieve. The funnel was replaced with a Drierite tube. An exotherm to ≈ 55° was observed, and some solid remained. After 19 hours of stirring the suspension was poured into a mixture of 150 ml of water and 30 ml of ice and stirred for 15 minutes. It was then treated with sodium carbonate monohydrate until evolution of carbon dioxide ceased (pH = 8). Then 40 g of ice was added, the mixture stirred until the ice just melted, the product filtered, washed with water, and dried at 90°/30 torr/1 hour to obtain 5.35 g (64%) of pale tan needles, mp 162.5-163.5°; ir: ν 3330, 2920 (w), 2830 (w), 1675 (sh), 1620 (sh), 1590, 1573, 1505, 1473, 1438, 1415, 1405, 1356, 1305, 1220 (br), 1170, 1105, 1095 (sh), 1020, 985, 833, 809, 752, 708, 640; pmr: δ 4.07 (s, 3H, OCH_3); 5.23 (d, J = 5Hz, 2H, CH_2N), 7.16 (d, J = 8Hz, 2H, Hs on phenyl *ortho* to OCH_3), 8.15 (d, J = 8Hz, 2H, Hs on phenyl *ortho* to C=O), 8.66 (d, J = 6Hz, 3H, Hs on pyridine *ortho* to C=O and NH), 8.90 ppm (d, J = 6Hz, 2H, Hs on pyridine *meta* to C=O).

Anal. Calcd. for $C_{15}H_{14}N_2O_3 \cdot 1/2H_2O$: N, 6.06. Found: N, 6.10.

Method B. From the Phenacylammonium Bromide (**33**).

The procedure in A. was carried out on 0.141 mole of **33**, resulting in 21.5 g (57%) of tan solid, mp 159-162.5°.

5-(4-Methoxyphenyl)-2-(4-pyridyl)oxazole (**2**).

Method A: Direct from Isonicotinic Acid.

A slurry of isonicotinic acid (3.48 g, 0.028 mole, Aldrich I-1,750-8), 4'-methoxyphenacylammonium chloride (5.42 g, 0.027 mole) and 30 ml of phosphorus oxychloride was boiled under reflux with stirring for 6 hours. Almost everything had dissolved after 2 hours; near the end of the heating period new solid began to precipitate. The mixture was cooled, and the excess phorphorus oxychloride was removed under reduced pressure on a rotary evaporator. With cooling and stirring, the residue was dissolved in 60 ml of cold 2:1::ethanol:water and made basic with 28% ammonia, followed by addition of 80 ml of water. The precipitated solid was filtered, washed well with water, and dried to give 6.36 g of product, mp 106-107°. Recrystallization from 300 ml of cyclohexane with carbon furnished 4.85 g (72%) of pale yellow solid, mp 108-109°, identical except for purity with the material made by the 2-step procedure below.

Method B: By Action of Phosphorus Oxychloride on the Amide.

The amide (**2**-amide, 5.00 g, 0.0185 mole) and 50 ml of phosphorus oxychloride (redistilled, bp 105-106°) were refluxed gently with magnetic stirring under an air condenser bearing a Drierite tube for 2.5 days. The residue after evaporation was dissolved in 50 ml of 1:1:: 2-propanol:water, becoming very hot. It was made basic with 10% sodium hydroxide, which caused the mixture to boil and to separate into two layers. The lower aqueous layer was discarded. The upper layer was diluted with water to 80 ml, cooled in ice, and treated with 10 ml of methanol. Product crystallized reluc-

tantly, was filtered, washed with water, and dried at 60°/30 torr/18 hours to give 4.0 g of brown solid. This was placed on a 2 cm high column of Aldrich 95% alumina, itself upon a 3 cm high column of Davison Grade 12 Silica in a medium Ace-Kau, and extracted with 80 ml of Freon TF until most blue-violet fluorescent material was eluted. The extract was cooled to 2°, and the lemon yellow solid was filtered, dried at 60°/30 torr/ 2hours to give 1.82 g (39%), mp 111.5-113°.

Method C: By Action of Acetic Anhydride and Phosphoric Acid on Amide.

The amide (**2**-amide, 21.0 g, 0.0778 mole) and 250 ml of acetic anhydride in a 500 ml round flask were warmed with stirring to ≈ 60° to effect partial solution, then 20 ml of 85% phosphoric acid was added, causing all solid to dissolve, and a second liquid layer to appear within 2 minutes. The mixture was heated to reflux for 1 hour, the stirring stopped, and the reaction allowed to cool to 22° overnight. The upper layer was discarded, and the orange solid remaining was warmed with 300 ml of water for an hour to obtain a stirrable suspension, which was cooled in an ice bath while 100 ml of 6*M* sodium hydroxide was added in 5 ml portions (pH = 6), followed by 1.5 hours of stirring. A granular solid appeared, which was filtered, washed with water, and dried at 70°/30 torr/24 hours; 17.5 g, mp 100-105° (with residue). This was extracted from a 5 cm high column of Aldrich 95% alumina in a medium Ace-Kau with 200 ml of Freon TF, and the extract was cooled to 0°, and the solid filtered, washed with 50 ml of cold Freon TF, and dried as before, producing 14.59 g of buff powder, mp 105-111°; ir: ν 1672 (C=O); pmr: δ 4.07 ppm (s, 3H, OCH_3), 7.21 (d, J = 9Hz, 2H, Hs *ortho* to Ar—O), 7.91 (d, J = 9Hz, 2H, Hs *meta* to Ar—O), 7.96 (s, 1H, H on oxazole), 8.76 (d, J = 6Hz, 2H, Hs *meta* to pyridine N), 9.06 (d, J = 6Hz, 2H, Hs *ortho* to pyridine N).

This material, 9.50 g, and Girard's Reagent T (3.36 g, 0.020 mole, Aldrich G90-O) with 5 ml of acetic acid in 100 ml of absolute ethanol were boiled under reflux for 1.5 hours. The mixture was treated with 50 ml of water, then 6*M* sodium hydroxide to discharge yellow color (pH = 8.5), and 55 ml of water, then kept at 0°. The large pale yellow spars were washed with 50% methanol and dried; 5.49 g, mp 110-112° (with residue); ir: ν 3020 (w), 2975 (w), 2930 (w), 2900 (w), 2840 (w), 1678 (w), 1645 (w), 1600, 1560, 1532, 1480, 1460, 1410, 1347, 1309, 1295, 1243 (s), 1211, 1173, 1130, 1058, 1017, 986, 942, 936, 830, 818, 712, 698.

This material plus a second crop of 2 g obtained by dilution of the above filtrates with 150 ml of water was recrystallized from 75 ml of 50% methanol at 22°, 6.77 g, mp 104-111°; recrystallized from 140 ml of cyclohexane with hot filtration, rosettes of nearly white needles, 5.38 g (57% rec.), mp 106-112°.

Method D. Action of Sulfuric Acid on the Amide.

To a 250 ml round bottom flask, equipped with an air condenser were added *N*-(4'-methoxyphenacyl)isonicotinamide (**2**-amide, 23.9 g, 85.7 mmoles) and 120 ml of concentrated sulfuric acid. The mixture was stirred for 45 minutes. It was quenched with 250 ml each ice and water, the mixture made basic with 28% ammonia, saturated with sodium chloride, and filtered. The yellow solid isolated was dried (32.5 g) and placed in large Ace-Kauffman column over 5 cm Alumina (Aldrich 19,997-4, Br•I, neut.) and extracted with Freon TF. The pot was cooled to -20° and the solid was filtered and dried to obtain 16.7 g (77%) of an off-white solid **2**, mp 112.5 - 114.5°; single spot on tlc developed with ethyl acetate, Rf = 0.48.

5-(4-Butoxyphenyl)-2-(4-pyridyl)oxazole (**3**).

The 4'-*n*-butoxyphenacylammonium chloride prepared in the same manner as **33** above was converted to the oxazole **3** by method B for **2**-amide above. A 6.5 hour reflux time with phosphorus oxychloride gave 77% of crude oxazole. Recrystallization from cyclohexane with carbon gave material of mp 84-85°.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.08; H, 6.38; N, 9.36.

4'-Fluorophenacylammonium Chloride.

Hexamethylenetetramine (**31**, 20.4 g, 0.146 mole) was dissolved in 500 ml of chloroform and treated with 4'-fluorophenacyl chloride (25.0 g, 0.145 mole) in 30 ml of chloroform. After 40 hours of reaction at room temperature, the mass of white felted needles which had crystallized was filtered, washed twice with chloroform and dried to give 43.0 g (95%) of salt (analogous to **32** in Figure 3), mp 130-135° to a red liquid.

All of this salt was dissolved in 480 ml of methanol. The solution was cooled in an ice-water bath before addition, in portions, of 66 ml of 12 *M* hydrochloric acid. A reaction time at ambient temperature of 17 days resulted in precipitation of ammonium chloride, which was filtered off and washed twice with cold ethanol. The combined filtrate and washings were taken to dryness on a rotary evaporator using a bath temperature of 25°. The residue was slurried with 50 ml of ice-cold water; the slurry was cooled at 5°; and the product was filtered, washed twice with ice-cold water, and dried to yield 13.8 g (53%), mp 236-239°dec. A repeat experiment gave 15.5 g (60%), mp 238-240°dec. The identity of this product was shown by its conversion to 2,5-bis(4-fluorophenyl)pyrazine and oxazole **4** below.

5-(4-Fluorophenyl)-2-(4-pyridyl)oxazole (**4**).

Isonicotinic acid (14.0 g, 0.114 mole, 20% excess) was converted to the acid chloride **34** with 55 ml of thionyl chloride in the usual manner. To this was added vacuum-dried 4'-fluorophenacylammonium chloride (17.6 g, 0.0921 mole), followed by 170 ml of dry pyridine. Protected by a drying tube, the mixture was stirred for 92 hours; then the pyridine was removed on a rotary evaporator at pump limit. The dark

gummy residue was slurried in 150 ml of 1:1::ethanol:water, made basic by carefully adding solid sodium carbonate, then diluted with 200 ml of water. The orange solid that separated was filtered, washed several times with water, and dried to yield 18.7 g of *N*-(4'-fluorophenacyl)isonicotinamide, mp soft 150°, 167-172°. This amide can be recrystallized from benzene, but was used without further purification in the next step.

Oven-dried amide (3.6 g) and phosphorus oxychloride (35 ml) were boiled under reflux with stirring for 16 hours; a homogeneous solution resulted. The excess phosphorus oxychloride was removed on a rotary evaporator. The black residue was dissolved in 50 ml of 3:7::ethanol:water and made basic with 10% sodium hydroxide. A black tar (0.4 g) separated first, follwed by a tan flocculent solid. The latter was filtered, washed well with water, and dried to give 2.4 g, which was recrystallized from 100 ml of 6:4::cyclohexane:benzene with carbon. The first material to crystallize (only a very small amount) proved to be 2,5-bis(4-fluorophenyl)pyrazine, mp 231.5-232.5°, after a recrystallization from dimethyl sulfoxide. See analog **57** in Figure 10.

Anal. Calcd. for $C_{16}H_{10}F_2N_2$: C, 71.63; H, 3.78; F, 14.17; N, 10.44. Found: C, 71.55; H, 3.85; F, 14.07; N, 10.39.

The desired oxazole **4** crystallized last, mp 152-153°.

Anal. Calcd. for $C_{14}H_9FN_2O$: C, 69.99; H, 3.78; N, 11.66. Found: C, 70.10; H, 3.84; N, 11.55.

4-Methyl-5-phenyl-2-(4-pyridyl)oxazole (**5**, see Figure 9).

Isonicotinic acid (25 g) was converted to its acid chloride **34** by stirring and boiling it under reflux with 35 ml of thionyl chloride for 30 minutes, cooling, and then stripping the excess thionyl chloride under reduced pressure.

To the resulting solid **34** was added phenylacetone oxime (**53a**, 14 g) dissolved in 40 ml of dry pyridine. The exothermic reaction was moderated by means of an ice/water bath. When the initial reaction was over, 10 ml of pyridine was added, and the mixture was stirred and boiled under reflux for 25 hours. Another exotherm occurred when reflux began. The solution was cooled, and the pyridine was removed on a rotary evaporator. The residue was dissolved in 50 ml of ethanol plus 25 ml of water, then the solution was made basic with 20 g of sodium hydroxide in 50 ml of water, with cooling and stirring. The mixture was diluted with 200 ml of cold water, and the product was extracted into methylene chloride (200 ml, then 2 x 50 ml). The extract was dried over sodium sulfate, filtered, and evaporated; 16.8 g of gum remained which partially crystallized. This gum was boiled with 300 ml of cyclohexane, cooled, diluted with 50 ml of *n*-hexane, and the mixture was cooled at -15° overnight. The supernatant was decanted from the tar; the latter was washed once with a small volume of cold (-15°) mixed solvent as above. Evaporating the combined liquids left 9.7 g (44% crude) of oxazole **5** as a tan solid. (An additional 0.9 g (4%) was isolated by reboiling the tar with 150 ml of cyclohexane, cooling, adding 25 ml of hexane, chilling at -15°, decanting and evaporating.)

Some of the crude product was further purified by boiling with *n*-hexane, decanting from tar, cooling to ambient temperature, stirring with carbon, filtering through Celite, and cooling the filtrate at 5° to obtain white grains, mp 89-90°. The pmr spectrum was consistent with expectations for oxazole **5**.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.48; H, 5.29; N, 11.90.

5-(4-Fluorophenyl)-4-methyl-2-(4-pyridyl)oxazole (**6**).

This compound was made in the same manner as in the previous example, except that the oxime **53b** of 4-fluorophenylacetone **52b** was used; yield 41%. After recrystallization from *n*-hexane with carbon, the compound melted at 121-123°.

Anal. Calcd. for $C_{15}H_{11}FN_2O$: C, 70.85; H, 4.36; N, 11.02. Found: C, 70.97; H, 4.42; N, 10.78.

4,5-Diphenyl-2-(4-pyridyl)oxazole (**7**).

Deoxybenzoin oxime **53c** was converted to the oxazole **7** in the manner used for oxazole **5** above. Oxazole **7** was not purified. Its identity was confirmed by conversion to the soluble tosylate quaternary salt, which was metathesized from 1:1::methanol:water as the perchlorate **7A** (Table 3), whose assays for C, H, and N were in agreement with theory.

4-Benzyl-5-phenyl-2-(4-pyridyl)oxazole (**8**).

This compound was made in low yield by the reaction of diphenylacetone oxime **53d** with isonicotinoyl chloride **34** in pyridine in the manner used for oxazole **5** above. It was isolated from the crude mixture by chromatography on silica by elution with chloroform. Recrystallization from *n*-hexane gave white silky needles, mp 128-129°.

Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.74; H, 5.16; N, 8.97. Found: C, 80.30; H, 5.24; N, 8.91.

Its identity was confirmed by conversion to the soluble tosylate quaternary salt, which was metathesized from 1:1::methanol:water as the perchlorate **8A** (Table 3), whose assays for C, H, and N were in agreement with theory. The previously unreported excitation maximum of **8A** of 381 nm and fluorescence maximum of 493 nm, both in ethanol, confirm the position of the 4-benzyl group by the close match of these maxima to those of the 4-methyl quaternary salt (392 and 494 nm) in ethanol (Ox **20** in [5]).

4-Chloro-5-phenyl-2-(4-pyridyl)oxazole (**9**).

Reaction of 5-phenyl-2-(4-pyridyl)oxazole (**1** in Figure 1, now available as Aldrich 22,903-2, mp 100-102°) was treated with *t*-butyl hypochlorite in chloroform at room temperature and in room light. Oxazole **9** precipitated as its hydrochloride salt, which was converted to the free base, mp 115-117°,

after recrystallization from ethanol/ water.

Its identity was confirmed by conversion to the tosylate quaternary salt **9A** (Table 3), whose assays for C, H, Cl and N were in agreement with theory.

N-(4'-*t*-Butyl-2',6'-dimethylphenacyl)phthalimide.

A solution of 4'-*t*-butyl-2',6'-dimethylacetophenone (49.51 g, 0.242 mole, Lancaster 6424) in 300 ml of acetic acid was treated with bromine dropwise (39.2 g, 12.6 ml, 0.245 mole, Aldrich 27,757-6) during 10 minutes. It was stirred 10 minutes after addition and worked up [33] to obtain 68.0 g (99%) of 4'-*t*-butyl-2',6'-dimethylphenacyl bromide as a slightly yellow oil of freezing point ≈ 0°.

The entire batch of bromo compound (68.0 g, 0.240 mole), in a 1000 ml flask with magnetic stirring in a heating mantle, was treated with 200 ml of DMF, then potassium phthalimide (48.9 g, 0.264 mole, Lancaster 2669). The mixture was heated at 95° for 2 hours, allowed to cool to 35°, diluted with 500 ml of water, stirred 10 minutes, and filtered. The solid was washed with 200 ml of 1:1::methanol:water, and dried at 120°/30 torr/2 hours to give 59 g of orange solid. This was recrystallized from 440 ml of acetic acid and 100 ml of water at 0°, washing the solid with 200 ml of 7:3::methanol:water, to give 37.5 g, mp 188-192°; prolonged cooling of the filtrates gave a 2nd crop of 5.7 g, mp 160-180°. Combined, the crops were recrystallized from 216 ml of acetic acid and 30 ml of water at 18°, yielding 35.6 g (42%), mp 193.5-195.5°. Its identity was confirmed by ultimate conversion to oxazole **10** below.

N-[2-(4'-*t*-Butyl-2',6'-dimethylphenyl)-2-oxoethyl]phthalamic Acid.

In a 2000 ml flask (foam!) were placed potassium hydroxide (6.87 g, 0.123 mole, 8.09 g of 85% U. S. P. pellets), 500 ml of water and 50 ml of 1-propanol. When complete solution was obtained with stirring, the above *N*-(4'-*t*-butyl-2',6'-dimethylphenacyl)phthalimide (35.6 g, 0.102 mole) was added, and the mixture was boiled under reflux for 3 hours. The hot liquid was decanted from a small amount of solid into a beaker, cooled in ice, and made acidic to *p*H = 2 with 6 *M* hydrochloric acid. The resulting gummy solid remaining after decantation of acid was triturated in a mortar with 200 ml of 95% ethanol. The more granular suspension was stirred rapidly with a propellor for a few minutes, filtered, the solid washed with water, and dried at 100°/30 torr/2 hours to give 36.3 g (97%), mp 157-158.5°. Its identity was confirmed by ultimate conversion to oxazole **10** below.

4'-*t*-Butyl-2',6'-dimethylphenacylammonium Bromide.

The entire batch of *N*-[2-(4'-*t*-butyl-2',6'-dimethylphenyl)-2-oxoethyl]phthalamic acid (above, 36.3 g, 0.099 mole) was boiled under reflux with 400 ml of 48% hydrobromic acid and 100 ml of acetic acid for 16 hours. The clear solution was allowed to cool somewhat, and all acids evaporated at 40 torr and 70° bath temperature. The residue was recrystallized from 500 ml of 2-propanol at 0° to give 18.74 g (63%) of shiny plates, mp 267-271°dec. Its identity was confirmed by ultimate conversion to oxazole **10** below. A second crop was obtained at -20°, 1.45 g (5%), mp 248-262°dec.

N-(4'-*t*-Butyl-2',6'-dimethylphenacyl)isonicotinamide.

Into a 250 ml flask equipped with a stirring magnet, nitrogen inlet, thermometer, and Drierite tube were placed 4'-*t*-butyl-2',6'-dimethylphenacylammonium bromide (18.0 g, 0.0600 mole), isonicotinoyl chloride hydrochloride (**34**, 12.8 g, 0.0720 mole, Aldrich 22,875-3), and 120 ml of pyridine (pre-dried over 4A Mol. Sieve). Stirring was begun, and an exotherm to 45° was observed. Then the flask was placed in a heating mantle and held at 70° for 1 hour, during which time all solid disappeared. The reaction mixture was kept at room temperature overnight; it deposited large spars. The suspension was quenched in 360 ml of ice-cold water. Sodium carbonate monohydrate was added to attain a *p*H = 8, followed by 2 hours of stirring. The clean granular solid was filtered, washed with 200 ml of water, and dried at 80°/30 torr/16 hours to obtain 13.8 g (71% crude), mp soft 158°; 166-176°. Recrystallization from 300 ml of dibutyl ether with hot filtration gave 9.25 g (48%) of buff spars, mp 177-184° with possible liquid crystal state or change in crystalline form. Its identity was confirmed by conversion to oxazole **10** below.

5-(4-*t*-Butyl-2,6-dimethylphenyl)-2-(4-pyridyl)oxazole (**10**).

The *N*-(4'-*t*-butyl-2',6'-dimethylphenacyl)isonicotinamide prepared above (9.10 g, 0.0281 mole) and 91 ml of phosphorus oxychloride were heated gently under reflux using an air condenser bearing a Drierite tube overnight. The cooled mixture was quenched in 1500 ml of ice and 400 ml of 28% ammonia. The black tar obtained was extracted with 100 ml of methylene chloride, and the extract was dried with 10 g of sodium sulfate and passed through a 2.5 cm diameter, 5 cm high column of Aldrich 19,997-4 neut. Br•I alumina, followed by 100 ml of methylene chloride. The eluate was stirred with 2 g of carbon overnight, filtered, and evaporated to yield 6.0 g of oil. This was crystallized from 50 ml of 3:2::methanol:water at 0° to obtain a first crop of 3.89 g, mp 87-91°. Further cooling at -20° and some dilution with water gave a second crop of 0.30 g and a third crop of 0.31g. All three crops were combined and extracted from atop a 3 cm high column of alumina in a medium Ace-Kau with 80 ml of Freon TF. The extract was stirred with 0.9 g of carbon for 15 minutes, with improvement in color; evaporation gave 4.64 g of oil which was distilled through a micro-claisen to obtain 2.65 g of pale yellow gum, bp ≈ 186°/0.9 torr. Crystallization from methanol/water at -20° gave 2.45 g (29%) of pale spars, mp 92.5-94°; pmr on IBM-Bruker NR-80 (6% in deuteriochloroform): δ 1.30 ppm (s, 9H, -C(CH_3)$_3$), 2.30 (s, 6H, PhCH_3), 7.20 (s, 3H, Ph*H* 3 and 5 and Ox*H* 4), 7.90 (d, J = 7Hz, 2H, Py*H* 3 and 5), 8.72 (d, J = 7Hz, Py*H* 2 and 6).

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.15. Found: C, 78.74; H, 7.47; N, 9.00.

4'-Bromophenacylammonium Bromide (See Figure 3 for analogous reactants).

The reaction of 4'-bromophenacyl bromide (Aldrich D3,830-8) with hexamethylenetetramine (Aldrich H1,130-0, **31**) gave 94% of the crystalline quaternary salt (details as for the 4'-methoxy analog, **33**). Reaction of the salt with hydrobromic acid gave product in 65-68% yield as the dihydrate, mp 260°dec after recrystallization from 1-butanol.

Anal. Calcd. for $C_8H_9Br_2NO \cdot 2H_2O$: Bromide Ion 24.1. Found by Volhard Titration: Bromide Ion 24.1.

N-(4'-Bromophenacyl)isonicotinamide (See Figure 3 for analogous reactants).

Condensation of 4'-bromophenacylammonium bromide with isonicotinoyl chloride hydrochloride (Aldrich 22,875-3, **34**) in dry pyridine (details as for the 4'-methoxy analog, **2**-amide) gave up to 33%, mp 162-166.5° after recrystallization from 1-propanol. Its identity was confirmed by conversion to the oxazole directly below.

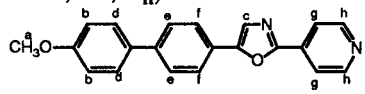
5-(4-Bromophenyl)-2-(4-pyridyl)oxazole (See Figure 3 for analogous reactants).

Dehydration of the *N*-(4'-bromophenacyl)isonicotinamide by means of acetic anhydride and 85% phosphoric acid gave the oxazole in 42% yield after recrystallization from heptane, mp 151.5-153.5° (details as for the 4'-methoxy analog, **2**). The analytical sample was obtained by recrystallization from heptane, mp 153-155.5°; ir: ν 1600, 1480, 830.

Anal. Calcd. for $C_{13}H_9BrN_2O$: C, 55.84; H, 3.01; Br, 26.53; N, 9.30. Found: C, 56.13; H, 3.19; Br, 26.29; N, 8.98.

5-(4'-Methoxy-4-biphenylyl)-2-(4-pyridyl)oxazole (**11**).

A Grignard reagent was prepared from 4-bromoanisole (Moore-Tec, 0.0051 mole, 0.95 g, 0.64 ml) and magnesium (Fisher M-11, 0.0051 mole, 0.124 g) in tetrahydrofuran (Aldrich 18,656-2, 20 ml). Reflux was continued for 2 hours after the last addition of 4-bromoanisole, then with heat removed, 0.060 g of palladium(II) chloride 1,4-bis(diphenylphosphino)butane catalyst was added, followed by 5-(4-bromophenyl)-2-(4-pyridyl)oxazole (0.00300 mole, 0.903 g). This caused a violent exotherm, which was followed up by an hour of deliberate reflux. After cooling a bit, 5 ml of 95% ethanol was added, the purple suspension was quenched in 40 ml of water, and the dilution kept at 2° for 3 days. Filtration, washing the precipitate with 50% methanol, and drying gave 0.97 g of crude product. Purification was accomplished by extraction of the crude from a 2 cm high column of alumina (Br I neut Aldrich 19,997-4) with 80 ml of cyclohexane in an Ace-Kauffman column to give 0.52 g, mp 212-215°. The extraction was repeated to obtain 0.42 g, mp 212-215°. Recrystallization from 15 ml of 1-butanol gave 0.38 g (40%), mp 213-215°; pmr, Varian XL200 (0.5% in deuteriochloroform): δ 1.67 ppm (s, sl br, 3H, H_2O), 3.88 (s, 3H, H_a), 7.01 (d, J_{bd} = 9.0Hz, 2H, H_b), 7.53 (s, 1H, H_c), 7.59 (d, J_{db} = 9.0Hz, 2H, H_d), 7.66 (d, J_{ef} = 8.6Hz, 2H, H_e), 7.79 (d, J_{fe} = 8.6Hz, 2H, H_f), 7.98 (d, J_{gh} = 6.0Hz, 2H, H_g), 8.79 (d, J_{hg} = 6.0Hz, 2H, H_h).



Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.48; H, 4.57; N, 8.42.

Chroman [17].

A 3-liter 3-necked flask on a heating mantle was equipped with magnetic stirring, a thermometer dipping into the mixture, a nitrogen inlet, a reflux condenser bearing a Drierite tube, and a powder funnel. Nitrogen flow and heating were begun, then 1200 ml of toluene was added, followed by 340 ml of a well-shaken 3.4 *M* solution in toluene of sodium bis(2-methoxyethoxy)aluminum hydride (1.16 mole, Aldrich 19,619-3, Red-Al®). The powder funnel was replaced by a liquid addition funnel containing 152 ml of 3,4-dihydrocoumarin (178 g, 1.20 mole, Aldrich D10,480-9). When the flask contents reached 65°, heat was turned off, and the lactone was added dropwise, generating an exotherm that caused boiling under reflux during the entire addition. Heat was applied to obtain a further 10 minutes of reflux, and the mixture was allowed to cool to 22° overnight. It was quenched in a mixture of 500 ml of 12 *M* hydrochloric acid, 1200 ml of water, 1200 ml of ice, and 300 ml of *t*-butyl methyl ether. The aqueous layer was extracted with 500 ml of *t*-butyl methyl ether; the organic layers were combined, washed with 1000 ml of 5% sodium bicarbonate solution, and the product was extracted into a mixture of 120 g of 50% w/w sodium hydroxide solution and 1800 ml of water. The extract was neutralized with ≈ 60 ml of 85% phosphoric acid (pH = 8), and the liberated product removed with 3 x 400 ml of *t*-butyl methyl ether. The ethereal solution was dried with 60 g of sodium sulfate, decanted into a tared flask, and evaporated to yield 167 g (92%) of 3-(2-hydroxyphenyl)propanol, a viscous pale orange liquid with a phenolic odor.

A 2-liter flask containing 3-(2-hydroxyphenyl)propanol (167 g, 1.10 moles) and 800 g of 85% phosphoric acid (Baker Reagent) was equipped with magnetic stirring, a T-head, and a condenser set for distillation, with the thermometer dipping into the liquid, which was heated with a mantle to 147° for 25 minutes, allowed to cool to 22°, then quenched in 2500 ml of water and 1000 ml of *t*-butyl methyl ether. The aqueous layer was extracted with 500 ml of *t*-butyl methyl ether, and the combined organic layers were washed with 600 ml of 1 *M* sodium hydroxide solution, followed by 100 ml of Claisen's alkali; dried with 60 g of sodium sulfate, decanted, and evaporated to give 121 g (82%) of chroman with a characteristic non-phenolic odor, d = 1.057g/ml at 22° (lit. [32a] d = 1.0610g/ml at 20°). The product of an earlier run, d = 1.065g/ml at 22°, was >95% pure as determined by gas chromatography on a silicone oil column.

A derivative, 6-acetylchroman, with mp 44.5-45.5° as reported [32b], was prepared by Friedel-Crafts reaction with acetyl chloride and aluminum chloride in 1,2-dichloroethane at 5°.

6-(Bromoacetyl)chroman.

Aluminum chloride (26.6 g, 0.220 mole, Fisher A-575) was weighed into a 500 ml flask containing a magnet, followed by 300 ml of 1,2-dichloroethane (Burdick and Jackson), and bromoacetyl chloride (25.0 ml, 47.2 g, 0.300 mole, Aldrich 20,955-4). The flask was capped with a Drierite tube, stirred to obtain complete solution, and placed in a freezer at -19°.

A 1-liter flask in a bath was equipped with magnetic stirring, nitrogen inlet, thermometer, air condenser with Drierite tube, and funnel. The flask was charged with chroman (25.2 ml, 26.8 g, 0.200 mole) and 200 ml of 1,2-dichloroethane. It was cooled by means of ice and methanol in the bath to 5°. The aluminum chloride solution in a liquid addition funnel was added below 5°, which required an hour. The burgundy-colored mixture was stirred an additional hour, and quenched in a mixture of 200 ml of water, 200 ml of ice, and 100 ml of 12 *M* hydrochloric acid; and stirred for 30 minutes The lower organic layer was washed with 400 ml of water, then 400 ml of 10% sodium carbonate solution; dried with magnesium sulfate, and evaporated to 51 g (100%) of liquid crude product. Its identity was confirmed by conversion to 2-(6-chromanyl)-2-oxoethylammonium bromide as given below.

The product of an earlier run utilizing bromoacetyl bromide would not crystallize on prolonged cooling in solvents at 2°.

2-(6-Chromanyl)-2-oxoethylammonium Bromide.

Lumps of hexamethylenetetramine (**31**, 28 g, 0.20 mole, MCandB) in a 1-liter conical flask were dissolved by magnetic stirring in 400 ml of chloroform, then a solution of 6-(bromoacetyl)chroman (51 g, 0.20 mole) in a mixture of 150 ml of Freon TF and 50 ml of methylene chloride was added. The quaternary salt analogous to **32** in Figure 3 began to separate in seconds, but the mixture was kept at 23° for 4 days. The salt was filtered, washed carefully on the Büchner with a thin stream of 200 ml of *t*-butyl methyl ether, and dried at 80°/30 torr/2 hours to give 61 g (77% yield based on chroman) of salt.

The salt was transferred to a 1-liter round flask with 500 ml of methanol, cooled in ice to 14°, and treated with 100 ml of 48% hydrobromic acid (Freeman Co.) dropwise with stirring during 5 minutes. Stirring was stopped after a clear solution was obtained in ≈ 2 hours, and the mixture was kept 3 days at 20°, then evaporated at a bath temperature of ≤35° to remove just the methanol, leaving a final volume of 175 ml of suspension, which was transferred to a beaker and cooled to -19° to complete the precipitation of product. The tan solid was filtered on sintered glass, washed with 50 ml of water saturated with ammonium bromide, and dried at 20°/0.1 torr/21 hours in a desiccator with sodium hydroxide pellets. The slightly damp solid was transferred to a 1-liter round flask with the aid of 250 ml each of absolute ethanol and benzene, and the solvents were evaporated to remove water as the ternary azeotrope. The residue was recrystallized from 500 ml of 1-butanol, filtering off ammonium bromide, and cooling to 0°; then again from 250 ml of 1-butanol, washing with 100 ml of *t*-butyl methyl ether, to yield 17.9 g (33%), mp 200-202°.

The analytical sample was obtained by recrystallizing 0.5 g from a previous run from 20 ml of 1-butanol twice, to obtain 0.32 g, mp 202-204°; ir: ν 3400, 3000 (vbr), 2950, 2920, 2900 (sh), 1674, 1605, 1568, 1550, 1495, 1480, 1440, 1366, 1319, 1258, 1188, 1167, 1141, 1062, 1050, 991, 928, 905, 876, 825; pmr: δ 2.15 (pentet, J = 6Hz, 2H, $CH_2CH_2CH_2$), 2.96 (t, J = 6Hz, 2H, $ArCH_2$), 4.43 (t, J = 6Hz, 2H, OCH_2), 4.90 (q, J = 6Hz, 2H, CH_2N), 6.98 (d, J = 9Hz, 1H, H8'), 7.46 (br, 3H, NH_3), 7.76 (dd, J = 2,9Hz,1H, H7'), 7.85 ppm (d, J = 2Hz, 1H, H5').

Anal. Calcd. for $C_{11}H_{14}BrNO_2$: C, 48.54; H, 5.18; Br, 29.37. Found: C, 49.11; H, 5.09; Br, 28.89.

N-[2-(6-Chromanyl)-2-oxoethyl]isonicotinamide.

A 300 ml round flask in a water bath was charged with 150 ml of pyridine (dried over 4A Molecular Sieve), then with isonicotinoyl chloride hydrochloride (**34**, 14.0 g, 0.0788 mole, Aldrich 22,875-3), then 2-(6-chromanyl)-2-oxoethylammonium bromide (17.9 g, 0.0656 mole), followed by brisk magnetic stirring for 44 hours. The mixture was quenched in 600 ml of 1:1::ice:water, and brought to *p*H 8 with sodium carbonate monohydrate; warmed to 40° in a water bath, and brought to *p*H 9, causing separation into 2 layers. The entire mixture was evaporated down to 400 ml, and kept at 22°. The crude product was filtered, washed with water, and dried at 50°/30 torr/18 hours, to give 15.6 g of crude product. This was recrystallized from 170 ml of toluene, cooled to 0°, to give 10.71 g, mp 138-141.5°, followed by recrystallization from 55 ml of methanol, cooled to 0°, to give dense tan prisms, mp 138.5-143.5°, then recrystallized from 100 ml of 50% methanol with the use of 0.3 g of carbon, followed by cooling at 22°, to give an oil* upon which colorless plates formed, 1.72 g (9%), mp 144.5-146.5°; ir: ν 3360, 3040, 2950, 2930, 2900, 2850, 1670 (sh), 1640 (br), 1601, 1578, 1530, 1490, 1430, 1405, 1354, 1313, 1245, 1182, 1158, 1133, 1061, 1023, 1003, 913, 875, 850, 811, 787, 759, 675; pmr: δ 2.15 ppm (quintet, J = 6Hz, 2H, $CH_2CH_2CH_2$), 2.95 (t, J = 6Hz, 2H, $ArCH_2$), 4.43 (t, J = 6Hz, 2H, OCH_2), 5.20 (d, J = 6Hz, 2H, CH_2N), 7.00 (d, J = 9Hz, 1H, H8'), 7.90 (dd, J = 2, 9Hz,1H, H7'), 7.95 (d, J = 2Hz, 1H, H5'), 8.60 (d, J = 6Hz, 3H, Hs *meta* to pyridine N and NH), 9.03 (d, J = 6Hz, 2H, Hs *ortho* to pyridine N).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.10; H, 5.47; N,9.39.

*The oil was crystallized from 160 ml of 50% methanol at

22° to give 5.50 g (28%), mp 139.5-143.5°.

5-(6-Chromanyl)-2-(4-pyridyl)oxazole (**12**).

In a 100 ml round flask on a mantle equipped with magnetic stirrer, were placed *N*-[2-(6-chromanyl)-2-oxoethyl]isonicotinamide (5.82 g, 0.0197 mole, typical mp 140-143°), and 50 ml of acetic anhydride (Aldrich 11,004-3, d = 1.079 g/ml at 22°). The suspension was warmed to obtain a clear solution, then 5.0 ml of 85% phosphoric acid (Baker Reagent) was added quickly, and the mixture was boiled under reflux for 1 hour, cooled well in an ice bath without stirring. The upper layer was decanted and discarded, and the lower was warmed with 50 ml of water in a mantle until stirrable; then, while cooling in a water bath, was made basic with 50 ml of 6 *M* sodium hydroxide. The resulting yellow solid, ≈ 5 g, mp 111-124°, was dissolved in 50 ml of warm absolute ethanol, treated with Girard's Reagent T (1.68 g, 0.0100 mole, Aldrich G90-0) and 3 ml of acetic acid, boiled under reflux for 1 hour, filtered while hot into a 200 ml beaker, diluted to 100 ml with water, treated with 6*M* sodi um hydroxide until *p*H = 8, diluted with water to 150 ml, and cooled in stages to -20°. The crude product was filtered, washed with a little 50% methanol, and dried at 70°/30 torr/6 hours to obtain 3.39 g of tan solid, mp 131-132.5° with residue. This was recrystallized from 68 ml of cyclohexane to give ≈ 3 g of a mixture of white and yellow crystals, mp 130-132.5°. (An infrared spectrum at this point showed no bands attributable to C=O or N-H.) The solid was taken up in 15 ml of methylene chloride and chromatographed on a 6 cm high 2 cm diameter column of neutral Br•I alumina (Aldrich 19,997-4). Methylene chloride (200 ml) eluted 1.00 g (18%), mp 130.5-133°. Ethyl acetate (150 ml) eluted 0.6 g (11%), mp 132.5-133.5°; ir: ν 3020 (w), 2935, 2850 (w), 1588, 1465, 1405, 1300, 1263, 1228, 1208, 1185, 1122, 1070, 1048, 1005, 987, 963, 827, 813, 698; pmr (deuteriochloroform): δ 2.08 (pentet, 2H, $CH_2CH_2CH_2$), 2.91 (t, J = 7Hz, 2H, $ArCH_2$), 4.26 (t, J = 5Hz, 2H, OCH_2), 6.87 (d, J = 9Hz, 1H, H8'), 7.36 (s, 1H, oxazole H) overlapping (m, 2H, H5' and H7'), 7.91 (d, J = 6Hz, 2H, Hs *meta* to pyridine N), 8.73 ppm(d, J = 6Hz, 2H, Hs *ortho* to pyridine N).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.57; H, 5.07; N, 10.07. Found: C, 73.62; H, 4.93; N,10.35.

5-(Bromoacetyl)coumaran.

This was prepared in the manner described above for the chroman homolog from 2,3-dihydrobenzofuran (14.45 g, 0.1200 mole, Aldrich 18,396-2), aluminum chloride (17.6 g, 0.132 mole, Fisher A-575), and bromoacetyl bromide (16 ml, 36 g, 0.18 mole, Aldrich B5,641-2). The product crystallized from 100 ml of methanol at -19°; and was recrystallized similarly to give 21.7 g (75%), mp 59-118°; lachrymator! Its identity was confirmed by conversion to 2-(5-coumaranyl)-2-oxoethylammonium bromide below.

2-(5-Coumaranyl)-2-oxoethylammonium Bromide.

Hexamethylenetetramine (**31**, 12.6 g, 0.0900 mole, MCandB) was magnetically stirred in a 400 ml tall beaker in 150 ml of chloroform until complete solution was obtained. Then a solution of 5-(bromoacetyl)coumaran (21.7 g, 0.0900 mole) in 50 ml of chloroform was added, which caused formation of a heavy precipitate in a few minutes; there was no further visible change after 10 minutes. After 5 hours, 100 ml of *t*-butyl methyl ether was added, filtered, washed with 100 ml of *t*-butyl methyl ether, and dried at 60°/30 torr/3 days to get 33.5 g (97%) of the quaternary salt analogous to **32**.

The salt was transferred to a 1-liter flask with the aid of 225 ml of methanol, the flask placed in a water bath, and 31 ml of 48% hydrobromic acid (Freeman Co.) was added, followed by 3 days of stirring. The clear amber solution was evaporated at bath temperature of ≤30° until the appearance of the first solid, transferred to a beaker, and kept at -19° overnight. The crude product was filtered on sintered glass, washed with a solution of 25 g of sodium bromide in 25 ml of water, and dried at 20°/0.2torr/3 days over potassium hydroxide pellets to get 24.5 g of tan solid, which was recrystallized from 250 ml of 1-butanol at -20°, filtered, washed with *t*-butyl methyl ether, and dried at 70°/30 torr/3 days, yielding 7.4 g (32%), mp 225-227°.

The analytical sample was prepared by recrystallizing 0.4 g from 16 ml of 1-butanol at 0°, decanting, and soaking in a minimum amount of 1-propanol for 3 days at 0° to obtain tan prisms, mp 230-232°, 0.23 g; ir: ν 3400 (br), 2920 (br), 2660, 2580, 1674, 1610, 1504 (s), 1489, 1460, 1385, 1304, 1275, 1261, 1162, 1122, 1003, 946, 900, 838; pmr: δ 3.37 (t, J = 8Hz, 2H, $ArCH_2$), 4.85 (t, J = 8Hz, 2H, OCH_2), 4.90 (q, J = 8Hz, 2H, CH_2N), 7.00 (d, J = 9Hz, 1H, H7'), 7.45 (br, 3H, NH_3), 7.95 ppm (m, 2H, H4' and H6').

Anal. Calcd. for $C_{10}H_{12}BrNO_2$: N, 5.43; Br, 30.96. Found: N, 4.96; Br, 30.57.

N-[2-(6-Coumaranyl)-2-oxoethyl]isonicotinamide.

This was prepared in the manner described above for the chroman homolog from 2-(5-coumaranyl)-2-oxoethylammonium bromide (7.0 g, 0.027 mole) to give 4.7 g of crude, mp 136-140°, which was recrystallized from 25 ml of methanol at 25°, then from 60 ml of toluene at 21°, to yield 2.07 g (27%).

The analytical sample was obtained by recrystallizing 0.2 g from 2 ml of toluene at 23° to get 0.2 g of nearly white small needles, mp 140-141.5°; pmr: δ 3.56 (t, J = 8Hz, 2H, $ArCH_2$), 5.06 (t, J = 8Hz, 2H, OCH_2), 5.41 (d, J = 6Hz, 2H, CH_2N), 7.23 (d, J = 9Hz, 1H, H7'), 8.23 (m, 2H, H4' and H6'), 8.85 (d, J = 6Hz, 3H, Hs *meta* to pyridine N and NH), 9.26 ppm (d, J = 6Hz, 2H, Hs *ortho* to pyridine N).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 69.23, 69.25; H, 5.12, 5.13; N, 10.21.

5-(5-Coumaranyl)-2-(4-pyridyl)oxazole (**13**).

This was prepared in the manner described above for the chroman homolog **12** from *N*-[2-(6-coumaranyl)-2-oxoethyl]isonicotinamide (1.9 g, 0.0067 mole) to give 1.10 g of crude, mp 158-164°. The solid was taken up in methylene chloride and chromatographed on a 4 cm high 2 cm diameter column of neutral 95% alumina (Aldrich). Methylene chloride (300 ml) eluted product, which, after evaporation of solvent, was recrystallized from 160 ml of cyclohexane to give pale yellow prisms, 0.84 g (47%), mp 161.5-164.5°.

The analytical sample was obtained by recrystallizing 0.2 g from 3 ml of 95% ethanol 3 times to give white product, mp 167-167.5°; ir: ν 3020, 2935, 2850 (w), 1588, 1464, 1408, 1300, 1262, 1230, 1206, 1184, 1121, 1069, 1048, 1005, 987, 962, 828, 813, 698; pmr (deuteriochloroform): δ 3.33 (t, J = 8Hz, 2H, ArCH_2), 4.71 (t, J = 8Hz, 2H, OCH_2), 6.93 (d, J = 9Hz, 1H, H7'), 7.41 (s, 1H, oxazole H), 7.60 (m, 2H, H4' and H6'), 7.95 (d, J = 6Hz, 2H, Hs *meta* to pyridine N), 8.76 ppm (d, J = 6Hz, 2H, Hs *ortho* to pyridine N).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 73.00; H, 4.40; N, 10.32.

N-[2,2-Diethoxy-2-(4-pyridyl)ethyl]-4-methoxybenzamide (**38** in Figure 4).

To a 250 ml, three necked, round-bottomed flask, equipped with an air condenser, a thermometer, drying tube, and magnetic stirring, were added triethylamine (10.1 g, (0.100 mole), 2,2-diethoxy-2-(4-pyridyl)ethylamine (**37**, [18], 10.5 g, 0.0500 mole), and 100 ml of dry toluene. To this was quickly added 4-methoxybenzoyl chloride (**36**, 8.53 g, 0.0500 mole, available from Aldrich). The solution turned yellow and a precipitate formed immediately. An exotherm raising the temperature to 60° was also observed. The reaction mixture was stirred overnight, filtered on a Büchner funnel, and the precipitate was washed with 20 ml of toluene. The precipitate was dissolved in 300 ml of chloroform and washed twice with 100 ml portions of water. The organic layer was dried over magnesium sulfate and concentrated to yield an off-white solid. Further drying (75°/30 torr/3 hours) gave 15.24 g (89%), mp 141.5-144°; single spot on tlc, R_f = 0.38 (ethyl acetate).

The compound was recrystallized from cyclohexane (filtered hot) prior to analysis, mp 142-143°; ir: ν 3250, 3046, 2972, 2931, 2893, 2840, 1650, 1605, 1562, 1513, 1462, 1436, 1410, 1350, 1307, 1254, 1173, 1122, 1102, 1059, 1029, 846, 827, 637, 555; pmr, Bruker NR-80 (deuteriochloroform): δ 1.25 (6H, t, J = 7 Hz, CH_3CH_2), 3.52 (4H, m, J = 7 Hz, CH$_3$CH_2), 3.84 (5H, m, N-CH_2 and CH$_3$-O), 5.75 (1H, s, br, NH), 6.88 (2H, d, J = 9 Hz, ArHs *ortho* to CH$_3$-O), 7.53 (4H, m, ArH *meta* to PyrN and CH$_3$-O), 8.64 ppm (2H, d, J = 5 Hz, ArHs *ortho* to PyrN).

Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.33; H, 7.02; N, 7.99.

N-[2-Keto-2-(4-pyridyl)ethyl]-4-methoxybenzamide (**14**-Amide).

To a 250 ml erlenmeyer flask, equipped with magnetic stirring, were added *N*-[2,2-diethoxy-2-(4-pyridyl)ethyl]-4-methoxybenzamide (**38**, 15.24 g, 0.0443 mole) and 150 ml of 1 *M* hydrochloric acid. The mixture was boiled for 15 minutes during which time a thick yellow precipitate formed. The mixture was boiled for an additional 15 minutes and then allowed to cool. After cooling, the reaction mixture was made basic with solid sodium bicarbonate and stirred overnight. Water was added to ensure complete solution of excess sodium bicarbonate, and the mixture was vacuum filtered, followed by vacuum drying (75°/30 torr/3 hours) to yield 11.5 g (96%) of a creamy yellow solid. The solid was recrystallized from absolute ethanol (0°), vacuum filtered, washed with 20 ml of cold (-20°) absolute ethanol, and dried for two hours as before to yield 9.83 g (82%) of light yellow crystals, mp 150-152.5°; single spot on tlc, R_f = 0.18 (ethyl acetate); ir: ν 3381(vbr), 1718, 1662, 1603, 1587, 1548, 1528, 1502, 1487, 1442, 1416, 1364, 1316, 1283, 1254, 1217, 1184, 1025, 833; pmr, Bruker NR-80 (deuteriochloroform): δ 3.90 (3H, s, CH$_3$-O), 4.98 (2H, d, CH$_2$), 6.98 (2H, d, J = 8.9 Hz, Ar*Hs ortho* to CH$_3$-O), 7.86 (4H, m, Ar*Hs meta* to PyrN and CH$_3$-O), 8.87 ppm (2H, d, Ar*Hs ortho* to PyrN).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.73; H, 5.17; N, 10.38.

2-(4-Methoxyphenyl)-5-(4-pyridyl)oxazole (**14**).

To a 100 ml round-bottomed flask, equipped with magnetic stirring, an air condenser, and a drying tube, were added 50 ml of thionyl chloride and 2.7 g (10 mmoles) of *N*-[2-keto-2-(4-pyridyl)ethyl]-4-methoxybenzamide (**14**-amide). The mixture was refluxed for 3 hours during which time the solution turned from yellow to red. The solution was cooled and poured into approximately 200 ml of ice. It was neutralized with concentrated sodium or potassium hydroxide to yield a tan solid. The solid was vacuum filtered, washed with a large amount of water, and vacuum dried overnight. The resulting tan solid was passed through a medium Ace-Kau containing 5 of cm silica over 5 of cm alumina with ethyl acetate as the solvent. The pot content was concentrated resulting in a greenish gray residue. This was recrystallized from 20 -25 ml ethyl acetate (carbon) at 0° to yield 1.86 g (74%) of a pale green solid, mp 171.5-174°; single spot on tlc, R_f = 0.29 (ethyl acetate); ir: ν 3095, 3036, 3007, 2982, 2951, 2902, 2842, 1610, 1580, 1499, 1488, 1457, 1438, 1426, 1416, 1310, 1260, 1216, 1188, 1178, 1140, 1109, 1067, 1023, 988, 956, 824, 742, 704, 692, 511; pmr, Bruker NR-80 (1.5% in deuteriochloroform): δ 3.90 (3H, s, CH$_3$-O), 7.02 (2H, d, J = 9 Hz, Ar*Hs ortho* to CH$_3$-O), 7.57 (3H, m, Ar*Hs meta* to PyrN and oxazole H), 8.07 (2H, d, J = 9 Hz, Ar*Hs meta* to CH$_3$-O), 8.67 ppm (2H, d, J = 5 Hz, Ar*Hs ortho* to PyrN).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.72; H, 4.67; N, 11.18.

In a second run, a fluorescent impurity of R_f = 0.36 (ethyl acetate) was removed by chromatography on silica, eluting

with 9:1::chloroform:acetonitrile, and collecting the second fluorescent fraction as **14**.

N-Isonicotinoyl-*N*'-(4-methoxybenzoyl)hydrazine (**15**-amide in Figure 5).

To a 500 ml, three-necked, round-bottom flask, equipped with a drying tube, magnetic stirring, powder addition funnel, and a thermometer, were added 100 ml of 1-methyl-2-pyrrolidinone (distilled and stored over 3A Molecular Sieve before use), 4-methoxybenzoyl chloride (**36**, 13.65 g, 0.0800 mole) and pyridine (11.85 g, 0.150 mole). The mixture was cooled to 0° in an ice bath. To this was added isonicotinic acid hydrazide (**39**, 10.0 g, 0.0730 mole) over a 45 minute period. Care was taken that the reaction temperature did not exceed 10°. Once addition was complete the mixture was allowed to stand at room temperature for 40 minutes, at which time the mixture color changed from green to brown. The mixture was then heated with a steam bath for 1 hour; the color changed to black. The mixture was then poured into ≈ 275 ml of an ice/water mixture. The resulting solution was vacuum filtered to yield 17.29 g (87%, crude) of a colorless precipitate after vacuum drying (90°/30 torr/3 hours), mp 200-203° (crude). The solid was recrystallized from 65 ml of benzonitrile, vacuum filtered, and washed by forming a suspension with 50 ml of toluene. The resulting colorless solid was dried in an Abderhalden pistol for 2.5 hours at 0.13 torr and 100° (water) to leave 16.37 g (83%) of solid, mp 201-203.5°; single spot on tlc, R_f = 0.66 (absolute ethanol).

An analytical sample was prepared by recrystallizing 1.35 g from 350 ml chloroform, mp 198-199°; ir: ν 3206 (br), 3016 (br), 2838, 1682, 1644, 1606, 1574, 1555, 1504, 1469, 1409, 1288, 1259, 1178, 1024, 843, 762, 750, 684; pmr, Bruker NR-80 (deuteriochloroform): δ 3.86 (3H, s, CH_3-O), 6.95 (2H, d, J = 9 Hz, Ar*Hs ortho* to CH_3-O), 7.92 (4H, m, Ar*Hs meta* to ArN and CH_3-O), 8.73 (2H, s, Ar*Hs ortho* to ArN), 10.27 (1H, s, anisoyl N*H*), 10.66 (1H, s, isonicotinoyl N*H*).

Anal. Calc. for $C_{14}H_{13}N_3O_3 \cdot 1/2\ H_2O$: C, 59.99; H, 5.03; N, 14.89. Found: C, 60.02; H, 4.65; N, 14.85.

2-(4-Methoxyphenyl)-5-(4-pyridyl)oxadiazole (**15**).

To a 250 ml round bottom flask, equipped with magnetic stirring, condenser, and a drying tube were added *N*-(4-methoxybenzoyl)-*N*'-(isonicotinoyl)hydrazine (**15**-amide, 15.0 g, 0.0553 mole) and 100 ml of thionyl chloride. The mixture turned a clear orange instantly. The mixture was refluxed for 3 hours, a heavy yellow precipitate quickly formed. The reaction mixture was concentrated and then dissolved in 250 ml of water. This was made basic (*p*H 14) with 6 *M* potassium hydroxide, the precipitate turned off-white. The precipitate was vacuum filtered to yield 17.42 g (crude) of off-white solid. The solid was extracted from a medium Ace-Kau packed with 4 cm of Davisil Grade 62 60-200 mesh silica over 4 cm of alumina with ethyl acetate as eluent. The extraction continued until no more fluorescent material was observed eluting from the column. The pot was cooled to -20°, and the contents vacuum filtered. After vacuum drying (78°/30 torr/3 hours), 10.6 g (76%) of a pale yellow solid was obtained, mp 193-195°; single spot on tlc, R_f = 0.37 (ethyl acetate); ir: ν 3092 (w), 3039 (w), 2989 (w), 2956 (w), 1848 (w), 1616, 1587, 1538, 1503, 1476, 1430, 1314, 1307, 1275, 1220, 1179, 1105, 1074, 1014, 840, 832, 743, 702, 507; pmr, Bruker NR-80 (deuteriochloroform): δ 3.91 (3H, s, CH_3-O), 7.07 (2H, d, J = 9 Hz, Ar*Hs ortho* to CH_3-O), 8.03 (4H, m, Ar*Hs meta* to ArN and CH_3-O), 8.80 ppm (2H, d, Ar*Hs ortho* to ArN).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.33; H, 4.37; N, 16.55.

2-(4-Methoxyphenyl)furan (**41** in Figure 6).

To a 1000 ml, three necked, round bottom flask, equipped with magnetic stirring, a thermometer, gas inlet with stopcock, and a pressure-equalizing addition funnel, were added furan (**40**, 10.2 g, 0.150 mole, dried over 3A Molecular Sieve) and dry tetrahydrofuran (150 ml, dried with sodium metal and benzophenone under nitrogen and distilled directly into reaction mixture, while keeping slight positive pressure with nitrogen gas). The reaction mixture was cooled to 0° and a 1.7 *M* *t*-butyllithium solution in pentane (88 ml, 0.150 mole, Aldrich 18,619-8) was added over a 30 minute period. A slight exotherm was observed and the color of the solution turned from colorless to orange with a small amount of light colored precipitate. After the mixture was stirred 2.5 hours, zinc chloride (20.5 g, 0.150 mole, dried by repeated melting with bunsen burner under vacuum) was added to the reaction mixture under nitrogen in a Glove Bag. An exotherm and effervescence were observed and the color of the solution changed from orange to brown. The reaction mixture was allowed to stand for 45 minutes with periodic shaking. To this mixture was added 250 ml of a dry tetrahydrofuran solution containing 4-bromoanisole (18.7 g, 0.100 mole) and then the coupling catalyst all at once (palladium(II) chloride 1,4-bis(diphenylphosphino)butane, 0.75 g, 1.25 mmoles). The reaction mixture was stirred for 20 hours at 50° under nitrogen, then quenched with 100 ml of 0.1 *M* hydrochloric acid. The layers were separated and the aqueous layer was washed 3 times with 100 ml portions of diethyl ether. The combined organic layers were then washed with a 100 ml portion of 5% sodium bicarbonate followed by three 100 ml portions of water. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield 23.2 g (crude) of a brown oil, which solidified into a brown solid. The solid was vacuum distilled, bp 70-95° and 124-104° at 0.15 torr to yield 16.76 g (96%) of yellow solid. This was recrystallized from 50 of ml methanol (carbon, -20°), vacuum filtered, and washed with 20 of ml methanol (-20°) to yield 13.35 g (77%) of colorless crystals after vacuum drying (20°/30 torr/3 hours), mp 53.5-55° (lit [20] mp 52-53°), single

spot on tlc, R_f = 0.69 (chloroform).

2-(4-Methoxyphenyl)-5-(4-pyridyl)furan (**16** in Figure 6).

A 3 necked, 100 ml round-bottomed flask, equipped with pressure-equalizing addition funnel, gas inlet, magnetic stirring and thermometer, was purged with nitrogen. To this was added 2-(4-methoxyphenyl)furan (**41**, 6.61 g, 38.0 mmoles) and 35 ml of dry THF (freshly distilled from sodium and benzophenone under nitrogen). The mixture was cooled to 0° and 22.4 ml of *t*-butyllithium (1.7 *M* in pentane, 38.0 mmoles, Aldrich 18,619-8) was added slowly keeping the temperature below 5°. During addition a precipitate formed. The mixture was stirred for an additional 3 hours at 0°. In a separate round bottom flask, dry zinc chloride (5.18 g, 38 mmoles, Cerac) was dissolved in 35 of ml dry THF (under nitrogen, in a glove bag). The zinc chloride solution (transferred *via* syringe) was added slowly to the furyllithium solution; an exotherm was observed. The solution was stirred and allowed to warm to room temperature over the next 1.5 hours, during which time all the precipitate dissolved.

To another 3-necked flask (250 ml), equipped with a pressure-equalizing addition funnel, gas inlet, magnetic stirring and thermometer, were added 70 of ml of dry THF and 4-chloropyridine hydrochloride (**42**, 3.80 g, 25.3 mmoles, Aldrich C7,022-3) under nitrogen. Methylmagnesium chloride (8.4 ml, 3 *M* in THF, 25.3 mmoles, Aldrich 18,990-1) was diluted with 30 of ml dry THF and added slowly to the mixture. A mild exotherm was observed along with the formation of methane. Most of the 4-chloropyridine hydrochloride dissolved and a precipitate of magnesium chloride formed. To this suspension, the furylzinc chloride solution was added *via* syringe in one portion, followed by the catalyst, palladium(II) chloride 1,4-bis(diphenylphosphino)-butane (0.23 g, 0.38 mmole). The mixture was heated to 50° at which time an exotherm to 65° was observed. The mixture was stirred at 50° for 20 hours, cooled to 0°, and quenched with 300 ml of water. The resulting suspension was filtered, re-suspended in water, made acidic with 12 *M* hydrochloric acid, and washed with 2 x 100 ml of methylene chloride. The organic layer (containing most of the unreacted starting material) was discarded. The aqueous layer was neutralized with ammonium hydroxide and saturated with sodium chloride. The mixture was filtered and the crude solid was washed with a copious amount of water, to yield a buff solid which was dried under vacuum at 70°, and extracted from a medium Ace-Kau column packed with 5 cm alumina with 200 ml of Freon TF as the eluent. The pot was cooled to -20° and the contents filtered to yield 4.06 g (64%) of pale yellow solid after drying, mp 148-150°, single spot on tlc, R_f (ethyl acetate) = 0.44.

The analytical sample was prepared by recrystallization from cyclohexane. Colorless rosettes resulted, mp 147-150°; ir: ν 3123, 3090, 3036, 3013, 2966, 2838, 1602, 1573, 1549, 1499, 1483, 1468, 1440, 1424, 1416, 1300, 1287, 1254, 1219, 1176, 1114, 1063, 1034, 1024, 988, 930, 834, 824, 799, 688, 510; pmr, Bruker NR-80 (deuteriochloroform): δ 3.85 (3H, s, O-CH_3), 6.63 (1H, d, J = 3.46 Hz, furyl H3), 6.95 (3H, m, ArH *ortho* to CH_3O- and furyl H4), 7.60 (4H, m, ArH *meta* to ArN and CH_3O), 8.60 ppm (2H, d, J = 5.56Hz, ArH *ortho* to ArN).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: N, 76.51; H, 5.30; N, 5.94.

2,6-Dimethylisonicotinoyl Chloride Hydrochloride (**55** in Figure 10).

Into a 100 ml tared flask were placed 2,6-dimethylisonicotinic acid (mp 283-288°dec [21a], 7.55 g, 0.0500 mole) and thionyl chloride (30 ml, Aldrich 15,780-5). The mixture was boiled under reflux for 1 hour, cooled to room temperature, and evaporated at room temperature, then at 50° bath temperature to leave 10.5 g of solid. Further drying at 20°/0.09 torr/2 hours left 10.13 g (98%), mp 148-151°. Its identity was confirmed by conversion to **56**-amide below.

N-(4-Methoxyphenacyl)-2,6-dimethylisonicotinamide (**56**-Amide).

To the freshly prepared 2,6-dimethylisonicotinoyl chloride hydrochloride (**55**, 10.1 g, 0.049 mole) were added 60 ml of pyridine and 4'-methoxyphenacylammonium bromide (**33**, 12.1 g, 0.0490 mole). This was stirred magnetically under a Drierite tube for 3 days after the exotherm to ≈ 50° subsided. It was necessary to scrape the sides with a bent spatula to make all solid dissolve. The reaction was quenched in 300 ml of water, using some methanol to aid transfer. The dilution was treated with sodium carbonate monohydrate in excess, kept at -2° for 6 hours, and filtered. The solid was washed with 150 ml of 1:1::methanol:water and dried at 70°/20 torr/18 hours to obtain 11.0 g (75%) of tan solid, mp 158-159.5°.

The analytical sample was obtained by recrystallizing 0.20 g from 5 ml of toluene with ≈ 50 mg of carbon, mp 161.5-162°, 0.13 g.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.36; H, 6.05; N, 9.43.

Attempted Preparation of 2-(2,6-Dimethyl-4-pyridyl)-5-(4-methoxyphenyl)oxazole (**56** in Figure 10).

The *N*-(4-methoxyphenacyl)-2,6-dimethylisonicotinamide (**56**-amide, 10.8 g, 0.0362 mole) with 130 ml of thionyl chloride was boiled under reflux for 3 hours and allowed to cool overnight. The excess thionyl chloride was removed under vacuum, and the residual black tar was treated with 100 ml of 1:1::ice:methanol. When the mixture became stirrable, 25 ml of 28% ammonia was added to give *p*H = 9. The new solid was filtered, washed with 100 ml of 1:1::methanol:water, and dried; mp 142-145°. An attempt to purify it by extraction from alumina in a small Ace-Kau with hexane led to decomposition. The extract was kept at -20° to obtain 2.59 of solid,

which was chromatographed on 20 g of EM Silica Gel 60, eluting with 3 ℓ of toluene to obtain ≈ 0.2 g of yellow solid. This was recrystallized from 15 ml of 1-propanol, 27 mg, mp 227-229°. Recrystallization from 5 ml of dibutyl ether gave pale needles, mp 227-229°, hazy, (lit transformation point 225-230°, [22]), which proved to be 2,5-bis(4-methoxyphenyl)pyrazine **57**, see **4** above; no oxazole was isolated); pmr, 250 MHz Bruker (0.7% in deuteriochloroform): δ 3.89 (s, 6H, -OCH_3), 7.04 (d, J = 9Hz, 4H, Hs *ortho* to -O-), 8.01 (d, J = 9Hz, 4H, Hs *meta* to -O-), 8.98 ppm (s, 2H, Hs on pyrazine).

2-(4-Pyridyl)cycloalkano[*d*]oxazoles

1-Tetralone-2-oxime (**44a** in Figure 7).

Potassium (12.5 g, 0.320 mole) was dissolved in *t*-butyl alcohol (200 ml) with stirring and refluxing. Ether (500 ml) was added, followed by dropwise addition of 1-tetralone (**43a**, 43.0 g, 0.294 mole) over a 10 minute period. Butyl nitrite (37 g, 0.36 mole) was added over a period of one hour. The solution was chilled with ice, and the precipitated red muddy salts were filtered and washed with ether. The salts were slurried with 400 ml of water and 40 ml of 12 *M* hydrochloric acid was added. The oxime was extracted with ether (800 ml), the extract was dried with magnesium sulfate, and concentrated to 100 ml. The solid was filtered to give 24.3 g (47% crude), mp 139-144° dec. Recrystallization from cold 95% ethanol gave 18.7 g (36%), mp 142-144° dec (lit [11] mp 138-140°); pmr (deuteriochloroform): δ 3.20 (4H, A_2B_2, Hs 3-4), 7.3-7.9 (3H, m, Hs 5-7), 8.30 (1H, dd, H8), 10.8 ppm (1H, br s, =NO*H*).

2-Amino-1-tetralone Hydrochloride (**46a**).

Into a 400 ml Parr bottle was placed 1-tetralone-2-oxime (**44a**, 13.15 g, 0.07506 mole), 130 ml of methanol and 0.5 g of palladium/barium sulfate catalyst. To this was added a solution of 13 ml of 12 *M* hydrochloric acid in 65 ml of water and 130 ml of methanol. The mixture was hydrogenated at 50 psi for 80 minutes after which there was no further uptake. The catalyst was filtered, and the filtrate was evaporated to dryness to leave a solid (14.2 g) which was recrystallized from ethanol to give 5.37 g. Concentration gave a second crop of 2.08 g, total 7.45 g (50%) of **46a**. This grey product had to be recrystallized from ethanol or 2-propanol containing a little hydrochloric acid until completely white.

Further concentration of the second ethanol filtrate gave 2-amino-1-naphthol hydrochloride, which, when neutralized with base gave needles, mp dark 90°, 138-140° dec. Its identity as **45a** was confirmed by its solubility in base, and 1H nmr spectrum in DMSO-d_6: δ 5.9 ppm (2H, v br, -NH_2), 7.0-8.3 (6H, m, Ar*H*), the -OH too broad to be seen; and its characteristic behavior on treatment with base — green solution with violet precipitate [34].

Isonicotinamide of 2-Amino-1-tetralone (**17**-Amide).

Isonicotinic acid (1.47 g, 0.012 mole) was boiled under reflux with 5 ml of thionyl chloride for 1 hour. The excess thionyl chloride was removed under vacuum, and the residual acid chloride **34** was added all at once to a solution of 2-amino-1-tetralone hydrochloride (**46a**, 1.97 g, 0.0100 mole) in 25 ml of pyridine, producing an exotherm to 45°. The mixture was stirred for a few minutes to dissolve all solid, then kept at room temperature for 2 hours. The pyridine was removed under vacuum, and the residue was treated with 60 ml of benzene and 40 ml of water. The mixture was made basic with 10% sodium hydroxide; the benzene layer separated, washed with water, and dried over magnesium sulfate. Evaporation gave 2.1 g of crude solid which was recrystallized from a little benzene to give 1.31 g (50%), mp 144-146°.

A second recrystallization from benzene gave the analytical sample, mp 145.5-146.5°; ir (Nujol): ν 3260, 1690, 1645; pmr (deuteriochloroform): δ 2.13 (2H, t, J = 13 Hz, of d, J = 5 Hz, Hs 3,3), 2.7-3.6 (2H, m, Hs 4,4), 4.90 (1H, d, J = 13 Hz, of t, J = 5 Hz, H2), 7.3-8.4 (4H, m, Hs 5-8), 7.90, 8.97 (4H, A_2B_2, Hs 3',5', Hs 2',6' on pyridine), 8.97 ppm (1H, br s, -N*H*).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.36; H, 5.43; N, 10.52.

4,5-Dihydro-2-(4-pyridyl)naphtho[1,2-*d*]-1,3-oxazole (**17** in Figure 7).

Some 2-amino-1-tetralone isonicotinamide (**17**-amide, 1.14 g, 0.00429 mole) was placed in 12 ml of phosphorus oxychloride and boiled under reflux for 19 hours during which the amide dissolved. The excess phosphorus oxychloride was removed under vacuum, and the residue was treated with 12 ml of ethanol and 5 ml of water; then the mixture was made basic with 10% potassium hydroxide. On cooling, the product precipitated, and was filtered to give 0.77 g (72%) of the oxazole **17**, mp 129-130°; pmr (deuteriochloroform): δ 3.10 (4H, A_2B_2, Hs 3',4'), 7.3-7.9 (4H, m, Hs 5'-8'), 8.07, 8.93 ppm (4H, A_2B_2, Hs 3",5" and 2",6").

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.46; H, 5.18; N, 11.07.

6-Methoxy-1-tetralone-2-oxime (**44b**).

In 60 ml of boiling *t*-butyl alcohol was dissolved potassium (3.84 g, 0.0985 mole). Ether (150 ml) was added, followed by 6-methoxy-1-tetralone (15.87 g, 0.0900 mole). Butyl nitrite (11.1 g, 0.0932 mole) was added dropwise with stirring over a period of 30 minutes. The insoluble salts were washed with ether, slurried with 180 ml of water and then 15 ml of 12 *M* hydrochloric acid was added. The initially formed oil solidified, the solid was filtered, washed with water, and while still damp, recrystallized from 250 ml of ethanol to give 8.86 g, mp 165-166° dec. Concentration of the filtrate to 1/3 volume gave 2.06 g of additional product, totaling 10.92 g (59%).

A second recrystallization from ethanol gave the analytical sample, mp 168-171° dec; ir (Nujol): ν 3130 (v br), 1788;

pmr (DMSO-d_6): δ 3.05 (4H, A_2B_2, Hs 3,4), 3.94 (3H, s, -OC*H*$_3$), 6.9-7.3 (2H, m, Hs 5,7), 7.9-8.3 (1H, m, H 8), 12.67 ppm (1H, s, =NO*H*).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.39; H, 5.33; N, 6.76.

2-Amino-6-methoxy-1-tetralone Hydrochloride (**46b**).

The 6-methoxy-1-tetralone-2-oxime (**44b**, 8.01 g, 0.0390 mole) was placed in a solution of 240 ml of methanol, 32 ml of water and 8 ml of 12 *M* hydrochloric acid. To this was added 0.5 g of palladium/barium sulfate catalyst. The mixture was hydrogenated at 50 psi for 105 minutes, the catalyst filtered off, and the filtrate evaporated to dryness. The residue was recrystallized from 180 ml of 2-propanol containing 5 ml of 12 *M* hydrochloric acid. Chilling in ice gave 5.99 g of crude hydrochloride, mp 206.5-209° dec. The grey solid, apparently contaminated with 2-amino-6-methoxy-1-naphthol hydrochloride, was recrystallized from ethanol to give 3.00 g (34%) of white product, mp 217-218° dec.

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.03; H, 6.20; Cl, 15.57; N, 6.15. Found: C, 57.03; H, 6.44; Cl, 15.06; N, 6.01.

Isonicotinamide of 2-Amino-6-methoxy-1-tetralone (**18**-Amide).

Isonicotinic acid (2.20 g, 0.0179 mole) was boiled under reflux with 7.5 ml of thionyl chloride for 1 hour. The excess thionyl chloride was removed under vacuum, and the residual acid chloride **34** was added all at once to a solution of 2-amino-6-methoxy-1-tetralone hydrochloride (**46b**, 3.40 g, 0.0149 mole) in 60 ml of pyridine. The solution was stirred and warmed slightly to get everything in solution, kept 2 hours, and freed from pyridine under vacuum. The residue was treated with 15 ml of ethanol and 10 ml of water, and the resulting solution was made basic with 10% potassium hydroxide. The resulting precipitate was filtered and washed thoroughly with water and when dried the 2.30 g (43%) had mp 158-160°; ir (Nujol): ν 3260, 1682, 1647; pmr (deuteriochloroform): δ 2.10 (2H, t, J = 13Hz, of d, J = 5, Hs 3,3), 2.7-3.6 (2H, m, Hs 4,4), 3.93 (3H, s, -OCH_3), 4.87 (1H, d, J = 13 Hz, of t, J = 5, H2), 6.8-8.4 (3H, m, Hs 5,7,8), 7.7 (1H, br s, -N*H*), 7.90, 9.00 (4H, A_2B_2, Hs 3',5', Hs 2',6' on pyridine).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.09; H, 5.56; N, 9.36.

4,5-Dihydro-7-methoxy-2-(4-pyridyl)naphtho[1,2-*d*]-1,3-oxazole (**18** in Figure 7).

The 2-amino-6-methoxy-1-tetralone isonicotinamide (**18**-amide, 1.55 g, 0.00524 mole) was placed in 15 ml of phosphorus oxychloride and boiled under reflux for 44 hours; there was still solid in the mixture. The excess phosphorus oxychloride was removed under vacuum, and the residue was dissolved in 50 ml of 1:1::ethanol:water, and the solution was made basic with 10% potassium hydroxide. The precipitated solid was filtered to give the product as fine needles, mp 157-158°, 1.26 g (86%).

The analytical sample was obtained by recrystallization from 2-propanol, mp 158-158.5°; pmr (deuteriochloroform): δ 3.10 (4H, A_2B_2, Hs 3',4'), 3.93 (3H, s, CH_3O-), 6.8-7.8 (3H, m, Hs 5',7',8'), 8.08, 8.95 ppm (4H, A_2B_2, Hs 3",5" and 2",6").

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.38; H, 4.85; N, 9.97.

6-Fluoro-1-tetralone-2-oxime (**44c**).

Some 6-fluoro-1-tetralone (**43c**, [35]) was converted to the oxime by the method used above in 75% yield, mp 166.5-167.5° dec, after recrystallization from benzene as white plates and blades.

Anal. Calcd. for $C_{10}H_8FNO_2$: C, 62.17; H, 4.17; F, 9.84; N, 7.25. Found: C, 61.94; H, 4.18; F, 9.62; N, 7.25.

2-Amino-6-fluoro-1-tetralone Hydrochloride (**46c**).

The oxime (**44c**) was hydrogenated in ethanolic hydrochloric acid over 10% Pd/C to give 84% of product, mp 215-218° dec.

Anal. Calcd. for $C_{10}H_{11}ClFNO$: C, 55.69; H, 5.14; F, 8.81; N, 6.50. Found: C, 55.95; H, 5.54; F, 8.62; N, 6.25.

4,5-Dihydro-7-fluoro-2-(4-pyridyl)naphtho[1,2-*d*]-1,3-oxazole (**19** in Figure 7).

The 2-amino-6-fluoro-1-tetralone hydrochloride (**46c**, 2.0 g, 9.27 mmoles), isonicotinic acid (1.2 g, 9.75 mmoles) and 15 ml of phosphorus oxychloride were boiled under reflux with stirring for 6 hours. The excess phosphorus oxychloride was removed on a rotary evaporator, and the residue was dissolved in 50 ml of 3:2::ethanol:water with initial cooling. This solution was made basic with 15 *M* ammonia, diluted with 50 ml of water, and chilled overnight at 5°. The solid product was filtered, washed with water, and dried, 2.2 g (89% crude), mp 158-160°, sinters at 155°. After recrystallization from 190 ml of cyclohexane with carbon the mp was raised to 160-161°. The white felted needles gradually changed to a granular material.

Anal. Calcd. for $C_{16}H_{11}FN_2O$: C, 72.17; H, 4.16; F, 7.14; N, 10.52. Found: C, 72.46; H, 3.98; F, 7.16; N, 10.38.

Phenanthrenequinone.

Prepared exactly as described [36]; ir: ν 2965 (br, -CH), 1665 (st, C=O), 1582 (st, C=C), 1469, 1438, 1271, 1219, 1155, 1112, 1008, 954, 928, 752, 708, 658, 604; pmr, Varian VXR 300 MHz (deuteriochloroform): δ 7.45 (2H, dt, J = 1.0, 7.5 Hz), 7.71 (2H, dt, J = 1.5 Hz, 7.5), 8.00 (2H, d, J = 8.1 Hz), 8.17 ppm (2H, dd, J = 1.5 Hz, 7.8).

Phenanthrenequinone Monoxime [37].

Into 200 ml of 95% ethanol were mixed phenanthrenequinone (20.8 g, 0.100 mole) and hydroxylammonium chloride (7.0 g, 0.100 mole). The suspension was boiled under reflux for 4 hours. The new solid was filtered and washed with 50 ml of 95% ethanol to give 20.4 g (91% crude) of the monoxime, mp 160-162°. Recrystallization from 100 ml/g of

absolute ethanol gave 73% of yellow powder, mp 154-156°; ir: ν 3040 (br, -OH), 1674 (m, C=N), 1650 (m, C=O), 1595 (st, C=C), 1520, 1440, 1414, 1380, 1295, 1260, 1162, 1112, 1085, 1058, 1038, 976 (st, N—O), 898, 880, 840, 762, 744, 719, 668, 608; pmr, Varian VXR 300 MHz (deuteriochloroform): δ 7.43 (1H, dt, J = 1.2 Hz, 7.5), 7.49 (1H, dt, J = 1.2 Hz, 7.6), 7.51 (1H, dt, J = 1.2 Hz, 7.7), 7.77 (1H, dt, J = 1.2 Hz, 7.7), 8.08 (1H, d, J = 8.4 Hz), 8.16 (1H, d, J = 8.4 Hz), 8.33 (1H, dd, J = 1.5 Hz, 8.1), 8.38 (1H, dd, J = 1.5 Hz, 8.1), 17.04 ppm (1H, s).

9-Amino-9,10-dihydrophenanthrene-10-one Hydrochloride.

Into 40 ml of methanol were placed phenanthrenequinone monoxime (2.23 g, 0.0100 mole), 10 ml of water, 5 ml of 12 *M* hydrochloric acid, and 0.25 g of 5% palladium/carbon catalyst. The suspension was hydrogenated at 50 psi for 2 hours. The new grey solids were filtered and washed with absolute ethanol to afford 2.30 g of crude product mixed with catalyst. Attempts to separate the catalyst by recrystallizations from various solvents were unsuccessful. The mixture was used for the reaction below.

2-(4-Pyridyl)phenanthreno[9,10-*d*]-1,3-oxazole (**20**).

A sample of isonicotinic acid (1.23 g, 0.0100 mole) and the crude 9-amino-9,10-dihydrophenanthren-10-one hydrochloride above (2.45 g, 0.0100 mole) were added with stirring at room temperature to 80 ml of phosphorus oxychloride. The mixture was then boiled under reflux for 24 hours, cooled, and carefully poured into 300 g of ice with stirring. This aqueous mixture was then neutralized to *p*H 7 with 28% ammonia. The precipitate was filtered and recrystallized from hot dimethyl sulfoxide to yield 1.04 g (35%), mp 249-251°; the pmr data are given in Table 5; the ^{13}C nmr data are given in Table 6.

Anal. Calcd. for $C_{20}H_{12}N_2O$: C, 81.07; H, 4.08; N, 9.45. Found: C, 80.15; H, 4.08; N, 9.17.

Acenaphthenequinone (**48** in Figure 8).

Sodium dichromate dihydrate (65 g, 0.22 mole) was added with stirring to a beaker containing acenaphthene (**47**, 20 g, 0.11 mole), cerium(III) nitrate hexahydrate (1.08 g, 0.00300 mole), and 160 ml of glacial acetic acid during a period of 2 hours. During the addition, a steam bath was used to keep the reaction temperature within 37-41°. After the addition, the mixture was stirred at room temperature for 19 hours. A tar-like mass was obtained. To this was added 700 ml of water and then 100 ml of 10% sodium carbonate solution, followed by heating on a steam bath for 30 minutes. The solids were filtered and washed with water to give the crude acenaphthenequinone, which was dissolved in 250 ml of hot 40% sodium bisulfite solution. The solution was treated with carbon and Celite, filtered, and acidified with 12 *M* hydrochloric acid to give 7.3 g (36%), mp 254-257°; ir: ν 2940 (st, C-H), 1665 (st, C=O), 1600 (st, C=C), 1450, 1315, 1230, 1136, 1110, 970, 930, 770, 720, 666; pmr, Varian VXR 300 MHz (deuteriochloroform): δ 7.92 (2H, dd, J = 7.2 Hz, 8.4), 8.18 (2H, dd, J = 0.6 Hz, 6.9), 8.34 ppm (2H, dd, J = 0.6 Hz, 8.4).

Acenaphthenequinone Monoxime (**49**).

Acenaphthenequinone (**48**, 1.82 g, 0.0100 mole) and hydroxylammonium chloride (0.70 g, 0.010 mole) were boiled under reflux in 25 ml of 95% ethanol for 1 hour. The resulting precipitate was filtered and washed with 95% ethanol to give the monoxime, 1.64 g (83%), mp 223-226°; ir: ν 3020 (br, N-O-H), 1695 (st, C=N), 1632 (st, C=O), 1585 (st, C=C), 1410, 1262, 1205, 1170, 1086, 980 (st, N-O), 845, 820, 765; pmr, Varian VXR 300 MHz (DMSO-d_6): δ 7.80 (1H, dd, J = 7.2 Hz, 8.4), 7.86 (1H, t, J = 7.5 Hz), 8.05 (1H, d, J = 7.2 Hz), 8.17 (1H, d, J = 8.4 Hz), 8.34 (2H, d, J = 7.8 Hz), 12.37 ppm (1H, s).

9-Amino-9,10-dihydroacenaphthene-10-one Hydrochloride (**50**).

Acenaphthenequinone monoxime (**49**, 2.0 g, 0.010 mole) was placed in a solution of 40 ml of methanol, 10 ml of water and 2 ml of 12 *M* hydrochloric acid. To this was added 0.2 g of 5% palladium/carbon catalyst. The mixture was hydrogenated at 50 psi for 90 minutes, the catalyst was removed by filtration, and evaporation of the filtrate to dryness afforded 1.98 g (90%), mp 298-301°. Its identity was confirmed by conversion to **21**-amide below.

Isonicotinamide of 9-Amino-9,10-dihydroacenaphthene-10-one (**21**-Amide).

Isonicotinic acid (1.23 g, 10 mmoles) was boiled under reflux with 5 ml of thionyl chloride for 1 hour. The excess thionyl chloride was removed under vacuum. The resulting acid chloride was added all at once to a solution of 9-amino-9,10-dihydroacenaphthene-10-one hydrochloride (**50**, 1.98 g, 9.00 mmoles) in 25 ml of pyridine. The mixture was warmed slightly and stirred to get all the solids into solution. It was then allowed to cool to and remain at room temperature for 2 hours. The pyridine was removed under vacuum, and the residue was treated with 15 ml of ethanol and 30 ml of water. The solution was made basic with freshly made 10% potassium hydroxide, and the resulting beige and black precipitate weighing 0.84 g when dry was recrystallized from benzene to remove the black chips, affording 0.323 g (10%) of **21**-amide, mp 220-221°; ir: ν 3250 (st, N-H), 1714 (st, C=O), 1642, 1410, 1334, 1275 (m, C=N), 1220, 1178, 1100 (C—N), 1012, 986, 856, 829, 772, 698, 608; pmr, Varian VXR 300 MHz (deuteriochloroform): δ 5.79 (1H, d, J = 6 Hz), 6.02 (1H, dd, J = 6.5 Hz, 7.5), 7.55 (1H, d, J = 2.5 Hz), 7.56 (1H, d, J = 3.5 Hz), 7.6 (2H, d, J = 5 Hz), 7.68 (2H, dd, J = 1.8, 4.3 Hz), 7.77 (1H, dd, J = 3.2 Hz, 5.3), 7.82 (1H, t, J = 4.5 Hz), 8.74 ppm (2H, dd, J = 1.8, 4.3 Hz).

Diels-Alder Adduct **51**.

Method A. Direct Condensation of 9-Amino-9,10-dihydroacenaphthen-10-one Hydrochloride (**50**) with Isonicotinic Acid.

The crude hydrochloride (**50**, 1.96 g, 9.00 mmole) and isonicotinic acid (1.11 g, 9.00 mmole) were added with stirring at room temperature to 50 ml of phosphorus oxychloride. The mixture was boiled under reflux for 48 hours, cooled, and carefully poured into 300 g of ice. The resulting aqueous mixture was brought to *p*H 7 with 28% ammonia, and the precipitate was filtered to give 1.34 g (55% crude), which was recrystallized from dimethyl sulfoxide to give 0.68 g (28%) of **51** as a yellow powder, mp 302-304°; ir: ν 3020, 1592, 1536, 1480, 1400, 1308, 1200, 1168, 1140, 1122, 1098, 1030, 986, 812, 760, 664, 624, 600; identical with that of **51** prepared from **51**-amide below. The ^{1}H nmr data are given in Table 8, identical with that of **51** prepared from **51**-amide below.

Method B. From **51**-amide.

Compound **51** was also prepared from **51**-amide, of which 0.54 g (1.9 mmoles) was boiled under reflux with phosphorus oxychloride for 20 hours. The excess phosphorus oxychloride was removed under vacuum from the resulting suspension. The residue was treated with 40 ml of 1:1::ethanol:water, and the mixture was made basic with freshly made 10% potassium hydroxide, and the resulting precipitate was recrystallized from dimethyl sulfoxide to give 0.41 g (79%) of **51** as a yellow powder, mp 305-306°.

Anal. Calcd. for $C_{30}H_{18}N_2O$: C, 85.29; H, 4.28; N, 6.63. Found: C, 86.01; H, 3.86; N, 6.55.

1,2-Indanedione-2-oxime.

In a 1-liter flask equipped with a mechanical stirrer, liquid addition funnel, condenser bearing a drying tube, and gas inlet diffuser was placed 250 ml of anhydrous ether. The ether was saturated with hydrogen chloride while being cooled in an ice bath, then 1-indanone (25.32 g, 0.1916 mole) was added; all of it dissolved. Isoamyl nitrite (24.67 g, 0.2108 mole), in 25 ml of dry ether was added dropwise to the cold solution over a period of 25 minutes. A yellow solid precipitated. Benzene (250 ml) was added, and the solution was saturated with hydrogen chloride. The mixture was stirred in the ice bath for ≈ 4 hours and allowed to warm to room temperature overnight. The solvents were removed under vacuum to get rid of excess hydrogen chloride as well. The residue was heated with 500 ml of benzene and cooled. Filtration gave 26.95 g (87%), mp dark 195°, 204° dec. Its identity was confirmed by conversion, ultimately, to the salt **22A** (assays in Table 3).

2-Amino-1-indanone Hydrochloride.

The 1,2-indanedione-2-oxime prepared above (26.9 g, 0.167 mole) was placed in a mixture of 200 ml of methanol, 35 ml of water, and 35 ml of 12 *M* hydrochloric acid, followed by 1.0 g of 5% palladium/carbon. The mixture was hydrogenated for 2 hours. The catalyst was filtered, and the filtrate evaporated to dryness with the bath temperature below 70°. The solid was dissolved in 170 ml of absolute ethanol, the solution was saturated with hydrogen chloride and chilled to -10° to give a solid, which was washed with 40 ml of absolute ethanol saturated with hydrogen chloride to give 18.30 g (40%) of product. Its identity was confirmed by conversion, ultimately, to the salt **22A** (assays in Table 3).

2-(4-Pyridyl)indeno[2,1-*d*]oxazole (**22** in Table 2).

Isonicotinic acid (12.07 g, 0.0980 mole) and 2-amino-1-indanone hydrochloride as prepared above (18.0 g, 0.0981 mole) were boiled under reflux in 100 ml of phosphorus oxychloride for 4 hours. The excess phosphorus oxychloride was evaporated under vacuum (40 torr) with a bath temperature of 100°. To the residue was added 75 ml of ethanol and 75 ml of water, and the mixture was made strongly basic with 10% sodium hydroxide, volume 500 ml. The 21.7 g of tarry material which formed was dissolved in 190 ml of hot ethanol and filtered from a small amount of brown needles (probably isonicotinic acid). Cooling the filtrate to room temperature gave 2.01 g of black and brown solid. This was leached with 3 x 100 ml of hot carbon tetrachloride. On cooling the crude product was filtered; concentration of the filtrate to 150 ml and then 30 ml after carbon treatment gave 3 crops, which were slurried with a few ml of ethanol, leaving undissolved some granular crystals, 0.48 g, mp 169-172°. Recrystallization from ethanol at -10° gave 0.3195 g (1.4%), mp 170-172°. Its identity was confirmed by conversion to the salt **22A** (assays in Table 3).

5-Methoxy-1,2-indanedione-2-oxime.

The reaction was carried out in the same manner as for 1,2-indanedione-2-oxime above. After removal of the solvents and hydrogen chloride under vacuum, the residue was slurried with carbon tetrachloride. Filtration gave (97%), mp soft 190°, 197-198° dec. The analytical sample was obtained by recrystallization of 0.41 g from 20 ml of ethanol at room temperature.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.54; H, 4.74; N, 7.26.

5-Methoxy-2-amino-1-indanone Hydrochloride.

This was prepared in the same manner as 2-amino-1-indanone hydrochloride above up to the point when the mixed solvent and hydrogen chloride were evaporated. The residue was recrystallized from 150 ml of ethanol saturated with hydrogen chloride, cooling to room temperature, to give 65%, no definite mp.

Anal. Calcd. for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.65; N, 6.56; Cl, 16.59. Found: C, 56.22; H, 5.68; N, 6.44; Cl, 16.37.

6-Methoxy-2-(4-pyridyl)indeno[2,1-*d*]oxazole (**23** in Table 2).

This was prepared in the same manner as 2-(4-pyridyl)-indeno[2,1-*d*]oxazole (**22**) above, however, the material

insoluble in carbon tetrachloride, 0.51 g, mp 155-156°, was recrystallized from 30 ml of methanol at 0° to give 0.2572 g of flakes, mp 166-169° dec. identified as the isonicotinamide of 5-methoxy-2-amino-1-indanone; ir: ν 3140-3260 (br, N-H), 1668 (ketone C=O), 1612 (amide C=O).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 64.42, 64.64; H, 4.73, 4.79; N, 9.34, 9.34.

The material soluble in carbon tetrachloride was concentrated to obtain a fraction of 0.68 g which was recrystallized from methanol to give 0.26 g (2.6%), mp 184-185°, of **23** (no C=O in ir). Another recrystallization from 30 ml of methanol gave the analytical sample.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.64; H, 4.47; N, 10.51.

4,4-Dimethyl-2-(4-pyridyl)indeno[2,1-*d*]oxazole (**24** in Table 2).

This was prepared in the same manner as 2-(4-pyridyl)-indeno[2,1-*d*]oxazole (**24**) above from 2-amino-3,3-dimethyl-1-indanone hydrochloride and isonicotinic acid to obtain (72%), mp soft, 135°, 140-142°. To obtain an analytical sample, 0.378 g was recrystallized from 3 ml of ethanol at -10°, 0.24 g, mp 145.5-147°.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.34; H, 5.13; N, 10.53.

6-Methoxy-4,4-dimethyl-2-(4-pyridyl)indeno[2,1-*d*]oxazole (**25** in Table 2).

Isonicotinic acid (3.80 g, 0.0309 mole) and 2-amino-3,3-dimethyl-5-methoxy-1-indanone hydrochloride (7.46 g, 0.0309 mole) were boiled under reflux in 30 ml of phosphorus oxychloride for 2 hours. The excess phosphorus oxychloride was evaporated under vacuum (40 torr) with a bath temperature of 100°. To the residue was added 25 ml of ethanol and 25 ml of water, and the mixture was made strongly basic with 10% sodium hydroxide and diluted to 250 ml. The next day the solid was filtered and washed with water then dried to give 9.55 g, mp soft, 130°, 147-150°. It was recrystallized with carbon from 75 ml of ethanol at -10° to give 0.22 g of red solid, mp 270-275°, which was discarded. Concentration of the filtrate to 40 ml and cooling gave 4.21 g, mp 150-158°.

This was leached with 2 x 75 ml of hot carbon tetrachloride to give, after cooling to 0°, 2.14 g of tan needles, mp 168-169°. Recrystallization from methanol at -10° gave 1.195 g (13%) of **25**.

Anal. Calcd. for $C_{18}H_{16}N_2O_2 \cdot H_2O$: C, 69.66; H, 5.20; N, 9.03. Found: C, 65.77; H, 5.17; N, 8.50.

Its identity was confirmed by conversion to the salt **25A** (assays in Table 3).

General Syntheses of Quaternary Salts.

For an example of the reaction see Figure 1. For preparative details and assays see Table 3. In general 1.0-1.5 moles of quaternizing agent per mole of pyridine base were boiled under reflux. For the quaternary salts **2G** and **2K** the solvent was the quaternizing agent, and thus was present in large excess. In anticipation of a slow reaction 2.0 moles of quaternizing agent per mole of base **11** was employed. To avoid any chance of diquaternization, only 0.9 mole of quaternizing agent per mole of base **14** was employed. The ^1H nmr spectral data for many of the quaternary salts are given in Table 4, for **20A** in Table 7.

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REFERENCES AND NOTES

+ Present address: Texaco, Inc., Research & Development, P. O. Box 1608, Port Arthur, TX 77641.

++ Present address: Chemistry Department, Drexel University, Philadelphia, PA.

* To whom all correspondence should be addressed.

[1] D. G. Ott, F. N. Hayes and V. N. Kerr, *J. Am. Chem. Soc.*, **78**, 1941 (1956).

[2] L. A. Lee and R. A. Robb, *IEEE J. Quantum Elect.*, **QE-16**, 777 (1980).

[3] A. N. Fletcher, R. A. Henry, R. F. Kubin and R. A. Hollins, *Opt. Commun.*, **48**, 352 (1984).

[4] J. M. Kauffman, C. J. Kelley, A. Ghiorghis, E. Neister and L. Armstrong, *Laser Chem.*, **7**, 343 (1987).

[5] A. N. Fletcher, R. A. Henry, M. E. Pietrak and D. E. Bliss, *Appl. Phys.*, **B 43**, 155 (1987).

[6] K. Nagayoshi and Y. Sato, *Chem. Letters*, 1355 (1983).

[7] C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.*, **94**, 843 (1972).

[8] I. J. Turchi, *Oxazoles*, Wiley-Interscience, New York, NY, 1986, p 3.

[9] A. W. Ingersoll, *Org. Synth.*, Coll. Vol., **2**, 503 (1943).

[10] H. E. Baumgarten and J. E. Petersen, *Org. Synth.*, Coll. Vol., **5**, 909 (1973).

[11] W. G. Reifenrath and D. S. Fries, *J. Chem. Soc. C*, 288 (1967); F. Zymalkowski and H. J. Rimek, *Arch. Pharm.*, **294**, 581 (1961).

[12] L. S. Afanasiadi, I. N. Tur and P. B. Kurapov, *Khim. Geterosikl. Soedin.*, **21**, 479 (1985); English Translation.

[13] G. S. Reddy and M. V. Bhatt, *Indian J. Chem. Sect. B*, **20B**, 322 (1981).

[14] M. D. Barnett, G. H. Daub, F. N. Hayes and D. G. Ott, *J. Am. Chem. Soc.*, **82**, 2282 (1960).

[15] L. W. Deady, R. D. Topsam and J. Vaughn, *J. Chem. Soc.*, 2094 (1963).

[16] G. Brieger, D. Hachey and T. Nestrick, *J. Chem. Eng. Data*, **13**, 581 (1968).

[17] G. Baddeley, N. H. R. Smith and M. A. Vickars, *J. Chem. Soc.*, 2455 (1956).

[18] J. L. La Mattina and R. T. Suleske, *Org. Synth.*, **64**, 19 (1985).

[19] D. C. Ayres and J. R. Smith, *J. Chem. Soc. C*, 2737 (1968).

[20] A. Pelter, M. Rowlands and C. Clements, *Synthesis*, 51 (1987).

[21a] Y. Suzuki, *Yakugaku Zasshi*, **81**, 1204 (1961); *Chem. Abstr.*, **56**, 3445d (1962); [b] Wayne Feely, US Patent 2,991,285 (9 Sept 58); *Chem. Abstr.*, **56**, P7283g (1962); [c] F. Bonadies, F. Savagnone, and M. L. Scarpati, *Gazz. Chim. Ital.*, **108**, 87 (1978).

[22] E. Zbiral and J. Stroh, *Liebigs Ann. Chem.*, **727**, 231 (1969).

[23] J. H. Hall, R. A. Henry and R. A. Hollins, U. S. Reg. H753 (6 March 1990).

[24] C. A. Maryanoff, *Heterocyclic Compounds*, **45**, 384 (1986).

[25a] G. Ya. Kondrat'eva, *Khim. Nauka. Prom.*, **2**, 666 (1957); *Chem. Abstr.*, **52**, 6345 (1958); [b] G. Ya. Kondrat'eva, *Izv. Akad. Nauk USSR, Otd. Khim. Nauk*, 484 (1959); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 457 (1959); [c] P. B. Terent'ev, N. P. Lomakina, M. I. Rahimi, D. K. Riad, Ya. B. Zelikover and A. N. Kost, *Khim. Geterosikl. Soedin.*, 1225 (1980); *Chem. Abstr.*, **94**, 30072 (1981).

[26] J. D. Barnhurst, *J. Org. Chem.*, **26**, 4520 (1961).

[27] B. M. Krasovitskii, D. G. Pereyaslova, V. T. Skripkina, L. M. Yagupolskii and V. I. Popov, *Dyes Pigments*, **9**, 21 (1988).

[28] J. M. Kauffman and J. H. Bentley, *Laser Chem.*, **8**, 49 (1988).

[29] R. F. Kubin, R. A. Henry, M. E. Pietrak and D. E. Bliss, *Laser Chem.*, **10**, 247 (1990).

[30] P. Leggate and D. Owen, *Mol. Cryst.*, **4**, 357 (1968).

[31] J. M. Kauffman and C. O. Bjorkman, *J. Chem. Ed.*, **53**, 33 (1975).

[32a] R. E. Rindfusz, *J. Am. Chem. Soc.*, **41**, 665 (1919); [b] G. Chatelus, *Ann. Chim.* [12] 4, 505 (1949); *Chem. Abstr.*, **44** 1975c (1950).

[33] See ω-bromoacetylmesitylene in W. G. Dauben and J. B. Rogan, *J. Am. Chem. Soc.*, **78**, 4135 (1956).

[34] C. Liebermann and P. Jacobson, *Liebigs Ann. Chem.*, **211**, 55 (1882).

[35] N. L. Allinger and E. S. Jones, *J. Org. Chem.*, **27**, 70 (1962).

[36] R. Wendland and J. Lalonde, *Org. Synth.*, Coll. Vol. **4**, 757 (1963).

[37] P. P. Sorokin, and J. R. Lankard, *IBM J. Res. Dev.*, **11**, 148 (1967).