Polarized Ethylene. V. Synthesis of 1-Substituted Indolizine, Pyrazolo[1,5-*a*]pyridine, and Their Related Compounds Using Methoxyethylene Derivatives

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The reaction of pyridinium or isoquinolinium *N*-ylides with methoxy-substituted ethylenes gave the corresponding indolizine and pyrrolo[2,1-*a*]isoquinoline derivatives bearing acetyl, aroyl, cyano, ester group at the 1-position in one step. Pyrazolo[1,5-*a*]pyridine, pyrazolo[1,5-*a*]quinoline, and pyrazolo[5,1-*a*]isoquinolines were also synthesized in good yields from the corresponding aromatic *N*-imines and methoxyethylene derivatives.

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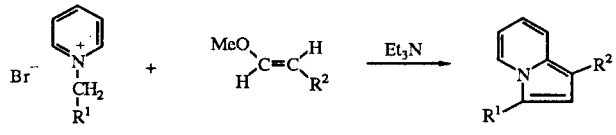
Indolizines are not only of practical but also of theoretical interest due to a delocalized 10π-electrons system [1-3]. Indeed, it is an important intermediates for drugs, dyestuffs, and light-screening agents in photographic emulsions. However, it is difficult to get only 1-acetyl- or 1-aroyl-substituted products on the indolizine ring by the Friedel-Craft reaction because of high and almost the same electron density at 1- or 3-positions [4]. The highly selective introduction of these useful functional groups at the 1-position of indolizine is a serious problem to solve in the indolizine chemistry [1-3]. We now report a new synthesis of 1-substituted indolizines by the 1,5-dipolar cyclization, but not by the Friedel-Craft's reaction.

In the proceeding paper of synthetic studies of indolizine derivatives, we have reported that 1-phenylthio-2-nitroethylene undergoes the 1,5-dipolar cyclization and that this can be conveniently applied to the direct synthesis of 1-nitroindolizine from the corresponding pyridinium *N*-ylides [5]. Despite of numerous papers with respect to indolizine synthesis by the 1,5-dipolar cyclization, the preparation of 1-acetyl- or 1-aroylindolizines was not so many and did not give good yields [6-8]. The present paper deals with a simple synthesis of 1-substituted indolizines, pyrazolo[1,5-*a*]pyridines, and their related compounds by the reaction of aromatic amine *N*-ylides and *N*-imines with methoxyethylene compounds.

We used methoxyethylene derivatives bearing only one electron-withdrawing group at β-position as polarized ethylene, instead of nitroolefin used for the preparation of indolizine derivatives. In general, bifunctionalized methoxyethylene compounds are commonly and versatilely used in organic synthesis. They reveal high reactivity toward various nucleophiles. Tamura, *et al.* also reported the synthesis of 1-acetylindolizines by the reaction of pyridinium *N*-ylides with methoxymethylacetylacetone [10,11]. This method, however, is insufficient for the synthesis of indolizine derivatives containing an acetyl group at the 1-position, leading to the poor yield of the desired products.

Scheme 1

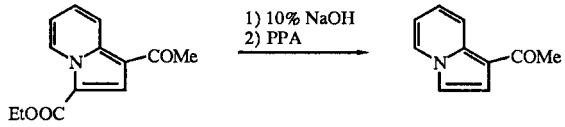


2a,b **1a-f** **3a-g**

2a: R^1 = COOEt
b: R^1 = CN

1a: R^2 = COMe
b: R^2 = COC_6H_5
c: R^2 = COC_6H_4-Br(*p*)
d: R^2 = COC_6H_4-OMe(*p*)
e: R^2 = CN
f: R^2 = COOMe

Scheme 2



3a **5**

At first we tried the synthesis of 1-acetylindolizines. The addition-elimination reaction of 4-methoxy-3-buten-2-one (**1a**) [12] with *N*-ylide **2a** occurred very smoothly at reflux in the presence of triethylamine in ethanol to give ethyl 1-acetylindolizine-3-carboxylate (**3a**) in 46% yield (Scheme 1). Deesterification of **3a**, thus obtained, using sodium hydroxide in methanol followed by treatment with polyphosphoric acid (PPA) gave the corresponding 1-acetylindolizine (**5**) in 67% yield (Scheme 2). Next this reaction was applied to the preparation of 1-aroylindolizines. 1-Aroylindolizine derivative **3b** was also obtained by the reaction of **2a** with **1b** under similar conditions of those described for the preparation of **3a**. The other 1-aroylindolizine derivatives **3c-d** were also synthesized from the corresponding 1-

acyl-2-methoxyethylenes **1b-d** [14-16] and pyridinium salts **2a,b**. Compounds **1e** and **1f** were also found to be useful reagents for the synthesis of indolizine derivatives **3e,f**. Namely, the reaction of the corresponding *N*-ylide (**2a**) with **1e** or **1f** gave the desired indolizines **3f,g** (Table 1).

Table 1

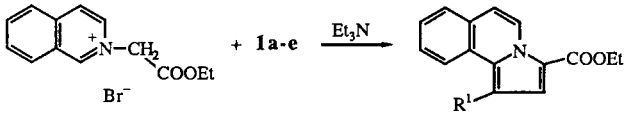
1,2-Disubstituted Indolizines

Product	R^1	R^2	mp(°)	Yield (%)
3a	COOEt	COMe	151	46
b	COOEt	COC_6H_5	116	58
c	COOEt	COC_6H_4-Br(*p*)	132	56
d	COOEt	COC_6H_4-OMe(*p*)	106	53
e	CN	COC_6H_5	138	44
f	COOEt	CN	75	63
g	COOEt	COOMe	123	22

The synthetic method of indolizine derivatives is applicable to prepare benzoindolizine and pyrrolo[2,1-*a*]isoquinoline derivatives. The reaction of **1a-f** with isoquinolinium salts **2c** gave the corresponding 1-acetyl- or 1-aroylpyrrolo[2,1-*a*]isoquinoline derivatives **4a-e** in moderate yields (Table 2).

Table II

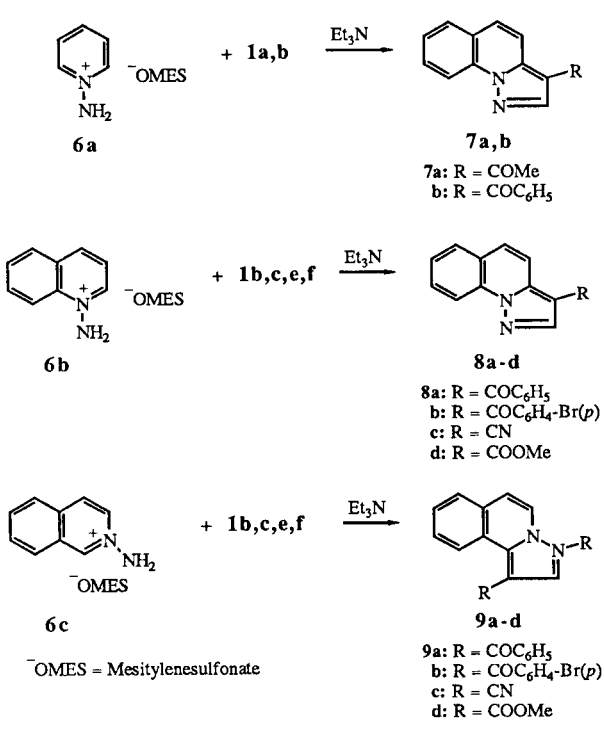
Ethyl 1-Substituted Pyrrolo[1,2-*a*] isoquinoline-3-carboxylates



Product	R^1	mp(°)	Yield (%)
4a	COMe	110	72
b	COC_6H_5	119	76
c	COC_6H_4-Br(*p*)	132	69
d	COC_6H_4-OMe(*p*)	151	51
e	CN	172	23
f	COOMe	138	32

1-Acetyl, 1-aroyl, 1-cyano, and 1-methoxycarbonylpyrazolo[1,5-*a*]pyridine, pyrazolo[1,5-*a*]quinoline, and pyrazolo[5,1-*a*]isoquinoline derivatives **7a-c**, **8a-d** and **9a-d** were also synthesized by the reaction of the corresponding aromatic *N*-imines with **1a-f** in good yields (Scheme 3).

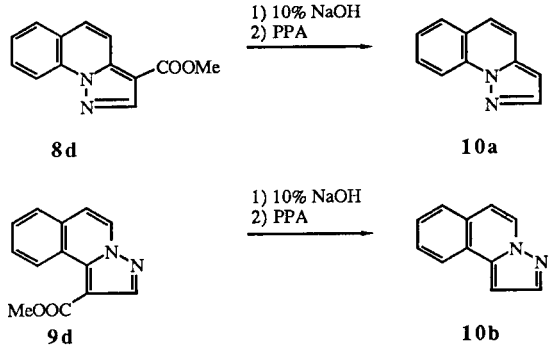
Scheme 3



⁻OMES = Mesitylenesulfonate

Compounds **8d** and **9d** are useful intermediates for the preparation of the corresponding parent compounds, pyrazolo[1,5-*a*]quinoline and pyrazolo[5,1-*a*]isoquinoline. Hydrolysis of the ester of **8d** and **9d** with sodium hydroxide in methanol to the corresponding carboxylic acids and subsequent decarboxylation of the acids at heating in PPA gave the desired compounds **10a** and **10b** in good yields (Scheme 4).

Scheme 4



In conclusion, the methoxyethylene compounds shown in this paper are very useful and convenient electrophilic reagents for the synthesis of 1-acetyl-, 1-aroyl, 1-cyano and 1-methoxycarbonylindolizines and their related compounds.

EXPERIMENTAL

All melting points were determined in capillary tubes and un-

corrected. Infrared (ir) spectra were recorded in potassium bromide pellets on a Shimadzu IR-640 spectrometer and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi EP-S2 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on JEOL JNM-FX-90Q (90 MHz) and JEOL JNM-PMX 60SI (60 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a JEOL JMS-01SG mass spectrometer.

Ethyl 1-Acetylindolizine-3-carboxylate (**3a**).

A solution of 0.10 g (1 mmole) of 4-methoxy-3-buten-2-one (**1a**), 0.246 g (1 mmole) of 1-ethoxycarbonylmethylpyridinium bromide (**2a**), and 0.3 ml of triethylamine in 20 ml of ethanol was refluxed for 9 hours. After removal of the solvent and excess of triethylamine, 30 ml of water was added to the residue and extracted with benzene (30 ml x 3). The combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on neutral alumina column using hexane:benzene (1:1) as an eluent to give 0.107 g (0.46 mmole) of **3a** as colorless needles in 46% yield. An analytical sample was recrystallized from ethanol to give colorless needles, mp 151°; ir (potassium bromide): ν 1688 (CO); uv (ethanol): λ max nm (log ϵ) 225 (4.22), 251 (4.52), 290 (4.12), 332 (4.30); ^{1}H nmr (deuteriochloroform): δ 1.43 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 2.57 (3H, s, CO-CH_3), 4.40 (2H, q, J = 7.0 Hz, O-CH_2-), 7.05 (1H, m, 6-H), 7.38 (1H, m, 7-H), 7.90 (1H, s, 2-H), 8.58 (1H, nd, J = 9.0 Hz, 8-H), 9.52 (1H, nd, J = 7.0 Hz, 5-H).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.47; H, 5.70; N, 6.07.

Ethyl 1-Benzoylindolizine-3-carboxylate (**3b**).

This compound (0.17 g, 0.58 mmole) was synthesized in 58% yield from 3-methoxy-1-phenyl-2-propen-1-one (**1b**) (0.162 g, 1 mmole) and 1-ethoxycarbonylmethylpyridinium bromide (**2a**) (0.264 g, 1 mmole) in a manner similar to that described for **3a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 116°; ir (potassium bromide): ν max cm^{-1} 1701, 1620 (CO); uv (ethanol): λ max nm (log ϵ) 220 (4.32), 249 (4.44), 333 (4.24), 345 (4.25), 358 (4.22); ^{1}H nmr (deuteriochloroform): δ 1.39 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 4.38 (2H, q, J = 7.0 Hz, O-CH_2-), 7.07 (1H, m, 6-H), 7.44 (1H, m, 7-H), 7.48-7.61 (4H, m, phenyl-H, 2-H), 7.79-7.89 (3H, m, phenyl-H), 8.63 (1H, nd, J = 8.7 Hz, 8-H), 9.56 (1H, nd, J = 6.8 Hz, 5-H).

Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.16; N, 4.78. Found: C, 73.41; H, 5.28; N, 4.65.

Ethyl 1-(4-Bromobenzoyl)indolizine-3-carboxylate (**3c**).

This compound (0.209 g, 0.56 mmole) was synthesized in 56% yield from 3-methoxy-1-(4-bromo)phenyl-2-propen-1-one (**1c**) (0.241 g, 1.0 mmole) and **2a** (0.296 g, 1 mmole) in a manner similar to that described for **3a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 132°; ir (potassium bromide): ν max cm^{-1} 1697, 1634 (CO); uv (ethanol): λ max nm (log ϵ) 220 (4.47), 251 (4.51), 330 (4.26), 347 (4.28), 359 (4.29); ^{1}H nmr (deuteriochloroform): δ 1.40 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 4.38 (2H, q, J = 7.0 Hz, -O-CH_2-), 7.09 (1H, m, 6-H), 7.45 (1H, m, 7-H), 7.68 (4H, m, phenyl-H), 7.73 (1H, s, 2-H), 8.62 (1H, nd, J = 9.0 Hz, 8-H), 9.58 (1H, nd, J = 7.0 Hz, 5-H).

Anal. Calcd. for $C_{18}H_{14}BrNO_3$: C, 58.09; H, 3.79; N, 3.76. Found: C, 57.66; H, 3.86; N, 3.48.

Ethyl 1-(4-Methoxybenzoyl)indolizine-3-carboxylate (**3d**).

This compound (0.154 g, 0.526 mmole) was synthesized in 53% yield from 3-methoxy-1-(4-methoxy)phenyl-2-propen-1-one (**1d**) (0.295 g, 1.2 mmoles) and **2a** (0.296 g, 1 mmole) in a manner similar to that described for **3a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 106°; ir (potassium bromide): ν max cm^{-1} 1698, 1634 (CO); uv (ethanol): λ max nm (log ϵ) 218 (4.39), 252 (4.47), 288 (4.11), 334 (4.35), 345 (4.35); ^{1}H nmr (deuteriochloroform): δ 1.40 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 3.90 (3H, s, OMe), 4.38 (2H, q, J = 7.0 Hz, O-CH_2-), 7.01 (2H, d, J = 9.0 Hz, 3',5'-H), 7.06 (1H, m, 6-H), 7.41 (1H, m, 7-H), 7.86 (2H, d, J = 9.0 Hz, 2',6'-H), 8.58 (1H, d, J = 9.0 Hz, 8-H), 9.57 (1H, nd, J = 7.0 Hz, 5-H).

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.17; H, 5.43; N, 4.27.

1-Benzoylindolizine-3-carbonitrile (**3e**).

A mixture of 0.24 g (2 mmoles) of bromoacetonitrile and 0.74 g (2.2 mmoles) of pyridine was heated at 40-50° for 30 minutes and then continued at 100° for 1 hour. The solid 1-cyanomethylpyridinium bromide (**2b**) was dissolved in 20 ml of ethanol and 0.162 g (1 mmole) of **1b** and 0.5 ml of triethylamine was added to this solution. The mixture was refluxed for 10 hours. After removal of the solvent and excess of triethylamine, 20 ml of water was added to the residue and extracted with benzene (20 ml x 2). The combined extract was dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on neutral alumina column using benzene as an eluent to give 0.190 g (0.443 mmole) of colorless crystals in 44% yield. An analytical sample was recrystallized from methanol to give colorless needles, mp 138°; ir (potassium bromide): ν max cm^{-1} 2210 (CN), 1641 (CO); uv (ethanol): λ max nm (log ϵ) 245 (4.50), 325 (4.12, shoulder), 346 (4.25); ^{1}H nmr (deuteriochloroform): δ 7.15-7.86 (7H, m, phenyl-H, 6,7-H), 7.63 (1H, s, 2-H), 8.40 (1H, nd, J = 7.0 Hz, 8-H), 8.62 (1H, nd, J = 9.0 Hz, 4-H), 7.63 (1H, s, 2-H).

Anal. Calcd. for $C_{16}H_{11}N_2O$: C, 77.72; H, 4.48; N, 11.33. Found: C, 77.81; H, 4.42; N, 11.32.

Ethyl 1-Cyanoindolizine-3-carboxylate (**3f**).

This compound (0.65 g, 2.8 mmoles) was synthesized in 63% yield from **2a** (1.23 g, 5 mmoles) and 3-methoxypropenenitrile (**1e**) (0.83 g, 10 mmoles) in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 75°; ir (potassium bromide): ν max cm^{-1} 2215 (CN), 1700 (CO): uv (ethanol): λ max nm (log ϵ) 223 (4.40), 244 (4.50), 257 (4.16), 266 (4.26), 323 (4.12), 329 (4.14): ^{1}H nmr (deuteriochloroform): δ 1.41 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 4.37 (2H, q, J = 7.0 Hz, O-CH_2-), 7.02 (1H, m, 6-H), 7.35 (1H, m, 7-H), 7.76 (1H, s, 2-H), 7.75 (1H, d, J = 8.8 Hz, 8-H), 9.52 (1H, d, J = 7.0 Hz, 5-H).

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.13; H, 4.81; N, 13.01.

Ethyl 1-Methoxycarbonylindolizine-3-carboxylate (**3g**).

A solution of 0.13 g (1.12 mmoles) of methyl 3-methoxyacrylate (**1f**), **2a** (0.246 g, 1 mmole), and 0.3 ml of triethylamine in 20 ml of acetonitrile was refluxed for 24 hours. After removal of the solvent and excess of the triethylamine, 30 ml of water was added to the residue and extracted with benzene (30 ml x 3). The combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on neutral

alumina column using a mixture of hexane and benzene (1:4) as an eluent to give 0.055 g (0.22 mole) of colorless needles in 22% yield. An analytical sample was recrystallized from ethanol to give colorless needles, mp 123°; ir (potassium bromide): ν max cm^{-1} 1703, 1693 (CO): uv (ethanol): λ max nm (log ϵ) 222 (4.33), 247 (4.57), 276 (4.26), 329 (4.24): ^1H nmr (deuteriochloroform): δ 1.41 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 3.91 (3H, s, OMe), 4.38 (2H, q, J = 7.0 Hz, O-CH_2-), 6.95 (1H, m, 6-H), 7.33 (1H, m, 7-H), 7.98 (1H, s, 2-H), 8.32 (1H, m, J = 9.0 Hz, 8-H), 9.51 (1H, nd, J = 7.0 Hz, 5-H).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.77; H, 5.34; N, 5.64.

Ethyl 1-Acetylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**4a**).

This compound (0.202 g, 0.72 mmole) was synthesized in 72% yield from **1a** (0.10 g, 1 mmole) and **2c** (0.296 g, 1 mmole) in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from ethanol to give pale yellow needles, mp 110°; ir (potassium bromide): ν max cm^{-1} 1692, 1659 (CO); uv (ethanol): λ max nm (log ϵ) 225 (4.33), 232 (4.34), 248 (4.36), 277 (4.64), 328 (4.06), 344 (4.18), 360 (4.18); ^1H nmr (deuteriochloroform): δ 1.45 (3H, t = 7.0 Hz, O-CH_2-CH_3), 2.72 (3H, s, CO-CH_3), 4.42 (2H, q, J = 7.0 Hz, O-CH_2-), 7.21 (1H, d, J = 7.5 Hz, 5-H), 7.26-7.71 (3H, m, 7,8,9-H), 7.97 (1H, s, 2-H), 9.38 (1H, d, J = 7.5 Hz, 6-H), 9.81 (1H, m, 10-H).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found: 72.45; H, 5.45; N, 4.82.

Ethyl 1-Benzoylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**4b**).

This compound (0.261 g, 0.76 mmole) was synthesized in 76% yield from **1d** (0.194 g, 1.2 mmoles) and **2c** (0.296 g, 1 mmole) in a manner similar to that described for **3a**. An analytical sample was recrystallized from ethanol to give pale yellow needles, mp 119°; ir (potassium bromide): ν max cm^{-1} 1703, 1648 (CO); uv (ethanol): λ max nm (log ϵ) 225 (4.39), 233 (4.41), 248 (4.42), 277 (4.72), 315 (4.03), 328 (4.15), 344 (4.26), 360 (4.33); ^1H nmr (deuteriochloroform): δ 1.38 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 4.38 (2H, q, J = 7.0 Hz, O-CH_2-), 7.26 (1H, d, J = 7.5 Hz, 6-H), 7.44-7.70 (7H, m, phenyl-H, 2,7,8,9-H), 7.90-8.01 (2H, m, phenyl-H), 9.02 (1H, m, 10-H), 9.42 (1H, d, J = 7.5 Hz, 5-H).

Anal. Calcd. for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 77.00; H, 5.14; N, 4.04.

Ethyl 1-(4-Bromobenzoyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**4c**).

This compound (0.290 g, 0.687 mmole) was synthesized in 69% yield from **1c** (0.241 g, 1.0 mmole) and **2c** (0.296 g, 1 mmole) in a manner similar to that described for **3a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 132°; ir (potassium bromide): ν max cm^{-1} 1707, 1649 (CO); uv (ethanol): λ max (log ϵ) 223 (4.20), 259 (4.58), 281 (4.62), 335 (4.01), 352 (4.11); ^1H nmr (deuteriochloroform): δ 1.47 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 4.38 (2H, J = 7.0 Hz, O-CH_2-), 7.26 (1H, d, J = 7.5 Hz, 6-H), 7.52-7.87 (8H, m, phenyl-H, 2,7,8,9-H), 9.04 (1H, m, 10-H), 9.67 (1H, d, J = 7.5 Hz, 5-H).

Anal. Calcd. for $C_{22}H_{16}BrNO_3$: C, 62.58; H, 3.82; N, 3.32. Found: C, 62.37; H, 3.84; N, 3.26.

Ethyl 1-(4-Methoxybenzoyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**4d**).

This compound (0.191 g, 0.512 mmole) was synthesized in 51% yield from **1d** (0.295 g, 1.2 mmoles) and **2c** (0.246 g, 1 mmoles) in a manner similar to that described for **3a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 151°; ir (potassium bromide): ν max cm^{-1} 1701, 1643 (CO); uv (ethanol): λ max nm (log ϵ) 225 (4.43), 256 (4.39), 281 (4.65), 335 (4.06), 352 (4.07); ^1H nmr (deuteriochloroform): δ 1.39 (3H, t, J = 7.1 Hz, O-CH_2-CH_3), 3.91 (3H, s, CH_3), 4.38 (2H, q, J = 7.1 Hz, O-CH_2-), 6.99 (2H, d, J = 8.79 Hz, 3',5'-H), 7.22 (1H, d, J = 7.47 Hz, 2',6'-H), 8.86 (1H, m, 10-H), 9.40 (1H, d, J = 7.47 Hz, 5-H).

Anal. Calcd. for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 73.82; H, 5.21; N, 3.74.

Ethyl 1-Cyanopyrrolo[5,1-*a*]isoquinoline-3-carboxylate (**4e**).

This compound (0.12 g, 0.46 mmole) was synthesized in 23% yield from **1e** (0.166 g, 2.0 mmoles) and **2c** (0.60 g, 2.0 mmoles) in a manner similar to that described for **3a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 172°; ir (potassium bromide): ν max cm^{-1} 2215 (CN), 1701 (CO): uv (ethanol): λ max nm (log ϵ) 225 (4.40), 238 (4.27), 267 (4.67), 286 (4.37), 311 (3.93), 323 (3.90), 338 (4.13), 355 (4.22): ^1H nmr (deuteriochloroform): δ 1.43 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 4.41 (2H, q, J = 7.0 Hz, O-CH_2-), 7.21 (1H, d, J = 7.7 Hz, 6-H), 7.60-7.74 (3H, m, 7,8,9-H), 8.94 (1H, m, 10-H), 9.29 (1H, d, J = 7.7 Hz, 5-H).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.51; H, 4.71; N, 10.47.

Ethyl 1-Methoxycarbonylpyrrolo[5,1-*a*]isoquinoline-3-carboxylate (**4f**).

This compound (0.096 g, 0.32 mmole) was synthesized in 32% yield from **2c** (0.296 g, 1.0 mmole) and **1f** (0.116 g, 1.0 mmole) in a manner similar to that described for the preparation of **3f**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 138°; ir (potassium bromide): ν max cm^{-1} 1709, 1685 (CO): uv (ethanol): λ max nm (log ϵ) 225 (4.32), 245 (4.37), 272 (4.67), 287 (4.40), 320 (4.00), 340 (4.15), 357 (4.21): ^1H nmr (deuteriochloroform): δ 1.43 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 3.96 (3H, s, OCH_3), 4.40 (2H, q, J = 7.0 Hz, O-CH_2-), 7.19 (1H, d, J = 7.47 Hz, 6-H), 7.56-7.72 (3H, m, 7,8,9-H), 8.04 (1H, s, 2-H), 9.39 (1H, d, J = 7.47 Hz, 5-H), 9.82 (1H, m, 10-H): ms: m/z 298 (M^+ + 1, 20), 297 (M^+, 100), 269 (10), 266 (18), 238 (34), 225 (14), 139 (11), 75 (11), 59 (30), 45 (17), 44 (24), 43 (40).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.58; H, 5.15; N, 4.79.

1-Acetyindolizine (**5**).

A solution of 0.10 g (0.43 mmole) of ethyl 1-acetylindolizine-3-carboxylate (**3a**) and 10% sodium hydroxide (sodium hydroxide 0.11 g, 1.96 mmoles) in 10 ml of methanol was refluxed for 3 hours. After removal of the solvent and water, *ca.* 2 g of polyphosphoric acid (PPA) was added to the residue and the mixture was heated at 100° for 1 hour. The reaction mixture was poured into 30 ml of ice-water, neutralized with sodium hydroxide solution and extracted with benzene (20 ml x 3). The combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on alumina column with a mixture of hexane and benzene (1:1) as an eluent to give 0.064 g (0.40 mmole, 93%) of a pale yellow viscous oil; ir (neat): ν max cm^{-1} 3110, 1641 (CO), 1529, 1507, 1485, 1430, 1367, 1238, 926; ^1H nmr (deuteriochloroform): δ 2.53 (3H, s, COMe), 6.75 (1H, m, 6-H), 7.02-7.22 (3H, m, 1,2,7-H), 8.01 (1H, nd, J = 6.8 Hz, 5-H), 8.43 (1H, bd, J = 8.7 Hz, 8-H); ms: m/z 159 (M^+, 48), 144

(M^+-15, 100), 130 (M^+-29, 4), 116 (15), 89 (41), 63 (14).

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.41; H, 5.81; N, 8.66.

1-Acetylpyrazolo[1,5-*a*]pyridine (**7a**).

A solution of 0.294 g (1 mmole) of 1-aminopyridinium mesitylenesulfonate (**6a**), 0.10 g (1 mmole) of **1a**, 0.3 ml of triethylamine in 15 ml of ethanol was refluxed for 5 hours. After removal of the solvent and excess triethylamine, 15 ml of ice-water was added to the residue and extracted with benzene (20 ml x 2). The combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on neutral alumina column using benzene as an eluent to give 0.060 g (0.375 mmole) of colorless needles in 38% yield. An analytical sample was recrystallized from ethanol to give colorless needles, mp 90°; ir (potassium bromide): ν max cm^{-1} 1651 (CO); uv (ethanol): λ max nm (log ϵ) 221 (4.39), 225 (4.42), 253 (3.79), 258 (3.80), 317 (4.09); ^1H nmr (deuteriochloroform): δ 2.56 (3H, s, $COCH_3$), 7.00 (1H, m, 6-H), 7.48 (1H, m, 5-H), 8.34 (1H, s, 2-H), 8.39 (1H, J = 8.8 Hz, 4-H), 8.54 (1H, nd, J = 6.8 Hz, 7-H).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.32; H, 5.28; N, 17.26.

1-Benzoylpyrazolo[1,5-*a*]pyridine (**7b**).

This compound (0.112 g, 0.504 mmole) was synthesized in 74% yield from **1b** (0.132 g, 0.816 mmole) and 1-aminopyridinium mesitylenesulfonate (**6a**) (0.200 g, 0.68 mmole) in a manner similar to that described for **7a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 95°; ir (potassium bromide): ν max cm^{-1} 1635 (CO); uv (ethanol): λ max nm (log ϵ) 221 (4.14), 226 (4.14), 250 (3.74), 327 (3.97); ^1H nmr (deuteriochloroform): δ 6.93 (1H, m, 6-H), 7.30-7.51 (5H, m, 2,5-H and phenyl-H), 7.63-7.87 (2H, m, phenyl-H), 8.23 (1H, d, J = 8.5 Hz, 4-H), 8.45 (1H, J = 7.0 Hz, 7-H).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.38; H, 4.69; N, 12.31.

3-Benzoylpyrazolo[1,5-*a*]quinoline (**8a**).

This compound (0.210 g, 0.77 mmole) was synthesized in 77% yield from **1b** from **1b** (0.194 g, 1.2 mmoles) and 1-aminoquinolinium mesitylenesulfonate (**6b**) 0.344 g, 1.0 mmole) in a manner similar to that described for **7a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 141°; ir (potassium bromide): ν max cm^{-1} 1632 (CO); uv (ethanol): λ max nm (log ϵ) 219 (4.28), 252 (4.15), 270 (3.88), 300 (3.73), 312 (3.84), 343 (4.14), 359 (4.10); ^1H nmr (deuteriochloroform): δ 7.46-7.97 (9H, m, phenyl-H, 5,6,7,8-H), 8.32 (1H, s, 2-H), 8.33 (1H, d, J = 9.2 Hz, 4-H), 8.67 (1H, nd, J = 7.4 Hz, 9-H).

Anal. Calcd. for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.45; H, 4.61; N, 10.27.

3-(4-Bromobenzoyl)pyrazolo[1,5-*a*]quinoline (**8b**).

This compound (0.337 g, 0.96 mmole) was synthesized in 96% yield from **2c** (0.241 g, 1.0 mmole) and **6b** (0.344 g, 1.0 mmole) in a manner similar to that described for **5a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 223°; ir (potassium bromide): ν max cm^{-1} 1633 (CO); uv (ethanol): λ max (log ϵ) 220 (4.58), 253 (4.45), 300 (4.01), 313 (4.11), 344 (4.44), 360 (4.40); ^1H nmr (deuteriochloroform): δ 7.71-7.87 (8H, m, phenyl-H, 5,6,7,8-H), 8.28 (1H, s, 2-H), 8.32 (1H, d, J = 7.8 Hz, 4-H), 8.65 (1H, d, J = 7.0 Hz, 9-H).

Anal. Calcd. for $C_{18}H_{11}BrN_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 61.55; H, 3.12; N, 7.99.

Pyrazolo[1,5-*a*]quinoline-3-carbonitrile (**8c**).

This compound (0.085 g, 0.44 mmole) was synthesized in 87% yield from **1e** (0.05 g, 0.60 mmole) and **6b** (0.172 g, 0.50 mmole) in a manner similar to that described for the preparation of **8a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 145°; ir (potassium bromide): ν max cm^{-1} 2220 (CN); ^1H nmr (deuteriochloroform): δ 7.56 (5H, m, 4,5,6,7,8-H), 8.28 (1H, s, 2-H), 8.62 (1H, d, J = 8.57, 9-H).

Anal. Calcd. for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.57; H, 3.88; N, 21.59.

Methyl Pyrazolo[1,5-*a*]quinoline-3-carboxylate (**8d**).

This compound (0.198 g, 0.88 mmole) was synthesized in 88% yield from **1f** (0.13 g, 1.12 mmoles) and **6b** (0.344 g, 1 mmole) in a manner similar to that described for the preparation of **8a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 149°; ir (potassium bromide): ν max cm^{-1} 1711 (CO): uv (ethanol): λ max nm (log ϵ) 213 (4.59), 223 (4.24), 253 (4.44), 258 (4.44), 292 (4.00), 304 (4.09), 330 (4.14), 345 (4.08); ^1H nmr (deuteriochloroform): δ 3.94 (3H, s, OMe), 7.43-7.90 (3H, m, 6,7,8-H), 7.69 (1H, d, J = 9.45 Hz, 5-H), 8.10 (1H, d, J = 9.45 Hz, 4-H), 8.43 (1H, s, 2-H), 8.62 (1H, d, J = 8.13 Hz, 9-H).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.82; H, 4.55; N, 12.38.

3-Benzoylpyrazolo[5,1-*a*]isoquinoline (**9a**).

This compound (0.216 g, 0.790 mmole) was synthesized in 79% yield from **1b** (0.194 g, 1.2 mmoles) and 1-aminoisoquinolinium mesitylenesulfonate (**6c**) (0.344 g, 1.0 mmole) and **2b** in a manner similar to that described for **5a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 158°; ir (potassium bromide): ν max cm^{-1} 1638 (CO); uv (ethanol): λ max nm (log ϵ) 220 (4.50), 253 (4.40), 275 (4.22), 334 (4.07), 348 (4.13); ^1H nmr (deuteriochloroform): δ 7.38 (1H, d, J = 7.3 Hz, 6-H), 7.45-7.98 (8H, m, phenyl-H and 7,8,9-H), 8.15 (1H, s, 2-H), 8.35 (1H, d, J = 7.3 Hz, 5-H), 9.47 (1H, m, 10-H).

Anal. Calcd. for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.42; H, 4.68; N, 10.10.

1-(4-Bromobenzoyl)pyrazolo[5,1-*a*]isoquinoline (**9b**).

This compound (0.332 g, 0.95 mmole) was synthesized in 95% yield from **1c** (0.241 g, 1.0 mmole) and **6c** (0.344 g, 1.0 mmole) and **2c** in a manner similar to that described for **7a**. An analytical sample was recrystallized from methanol to give pale yellow needles, mp 210°; ir (potassium bromide): ν max cm^{-1} 1644 (CO); uv (ethanol): λ max nm (log ϵ) 257 (4.45), 336 (4.13), 349 (4.18); ^1H nmr (deuteriochloroform): δ 7.29 (1H, d, J = 7.0 Hz, 6-H), 7.60-7.85 (7H, m, phenyl-H, 7,8,9-H), 8.21 (1H, d, J = 7.0 Hz, 5-H), 9.40 (1H, m, 10-H).

Anal. Calcd. for $C_{18}H_{11}BrN_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 61.38; H, 3.09; N, 7.88.

Pyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**9c**).

This compound (0.052 g, 0.27 mmole) was synthesized in 60% yield from **6c** (0.172 g, 0.5 mmole) and **1e** (0.042 g, 0.5 mmole) in a manner similar to that described for the preparation of **7a**. An

analytical sample was recrystallized from ethanol to give colorless needles, mp 147°; ir (potassium bromide): ν max cm^{-1} 2225 (CN); ^1H nmr (deuteriochloroform): δ 7.24 (1H, d, J = 7.25 Hz, 6-H), 7.67-7.81 (3H, m, 7,8,9-H), 8.25 (1H, s, 2-H), 8.31 (1H, d, J = 7.25 Hz, 5-H), 8.78 (1H, m, 10-H).

Anal. Calcd. for $C_{12}H_7N_2$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.30; H, 3.88; N, 21.45.

Methyl Pyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**9d**).

This compound (0.084 g, 0.37 mmole) was synthesized in 65% yield from **6c** (0.172 g, 0.5 mmole) and **1f** (0.09 g, 0.78 mmole) in a manner similar to that described for the preparation of **7a**. An analytical sample was recrystallized from ethanol to give colorless needles, mp 162°; ir (potassium bromide): ν max cm^{-1} 1707 (CO): uv (ethanol): λ max nm (log ϵ) 265 (4.54), 307 (3.61), 321 (3.85), 336 (3.93); ^1H nmr (deuteriochloroform): δ 3.96 (3H, s, OMe), 7.12 (1H, d, J = 7.25 Hz, 6-H), 7.68-7.31 (3H, m, 7,8,9-H), 8.28 (1H, d, J = 7.25 Hz, 5-H), 8.47 (1H, s, 2-H), 9.82 (1H, m, 10-H).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.17; H, 4.73; N, 12.87.

Pyrazolo[1,5-*a*]quinoline (**10a**).

A solution of 0.10 g (0.44 mmole) of methyl pyrazolo[1,5-*a*]quinoline-3-carboxylate (**8d**) and 10% sodium hydroxide (sodium hydroxide 1.0 g, 25 mmoles) in 30 ml of methanol was refluxed for 3 hours. After removal of the solvent and water, PPA (*ca.* 3.0 g) was added to the residue and the mixture was heated at 100° for 1 hour. The reaction mixture was poured into 100 ml of ice-water, neutralized with 10% sodium hydroxide solution and extracted with benzene (30 ml x 3). The combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed over alumina with a mixture of hexane and benzene (1:1) as an eluent to give 0.054 g of **10a** [5] as a pale yellow oil in 72% yield; ir (neat): ν max cm^{-1} 3080, 1619, 1502, 1452, 1395, 805: ^1H nmr (carbon tetrachloride): δ 7.33-7.90 (7H, m, 2,3,4,5,6,7,8-H), 8.54 (1H, m, 9-H): ms: m/z 169 ($M^+ + 1$, 10), 168 (M^+, 100), 140 (16), 128 (17), 119 (31), 117 (33), 43 (23); HRMS Calcd. for $C_{11}H_7N_2$ = 168.1976. Found: 168.0703.

Pyrazolo[5,1-*a*]isoquinoline (**10b**).

This compound (0.028 g, 0.17 mmole) was prepared in 77% yield form methyl pyrazolo[5,1-*a*]isoquinoline-3-carboxylate (**9d**) (0.050 g, 0.22 mmole) in a manner similar to that described for the preparation of **10a**. This product was purified by the alumina column chromatography with a mixture of hexane and benzene (1:1) as an eluent to give a pale yellow oil [lit 17, mp 61°]; ir (neat): ν max cm^{-1} 3075, 3060, 1640, 1580, 1537, 1476, 1438, 1373, 790, 739, 689: ^1H nmr (deuteriochloroform): δ 6.92 (1H, d, J = 4.5 Hz, 1 or 2-H), 6.96 (1H, d, J = 4.5 Hz, 2 or 1-H), 7.10-7.70 (4H, m, 6,7,8,9-H), 7.98 (1H, m, 10-H), 8.18 (1H, d, J = 7.0 Hz, 5-H); ms: m/z 168 (M^+, 25), 121 (31), 119 (96), 117 (100), 84 (14), 82 (21), 47 (17).

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