Synthesis and Regiospecificity in Methylation of Pyrido[1,2-*a*]pyrazinium-1- and 3-olates and Pyrido[1,2-*b*]pyridazinium-2- and 4-olates [1]

Sándor Bátori and András Messmer*

Central Research Institue for Chemistry, Hungarian Academy of Sciences,
H-1525 Budapest POB 17, Hungary

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New methods have been developed for the synthesis of pyrido[1,2-*a*]pyrazinium-1- and 3-olates **5a-f**, **9** and 1-thiolate **24** as well as of pyrido[1,2-*b*]pyridazinium-4- and 2-olates **14**, **20**. The methylation of these new compounds was studied by soft and hard methylating agents. Depending on the nature of the reagent used, the pyrido[1,2-*a*]pyrazinium-1-olates **5a-f** gave NMe **22a-f** and/or OMe **23a-f** products, whereas the 3-olate **9** and both the 4- and 2-pyridazinium-olates **14**, **20** afforded solely OMe compounds **10**, **15**, **21**. A selectivity rule for methylation is proposed.

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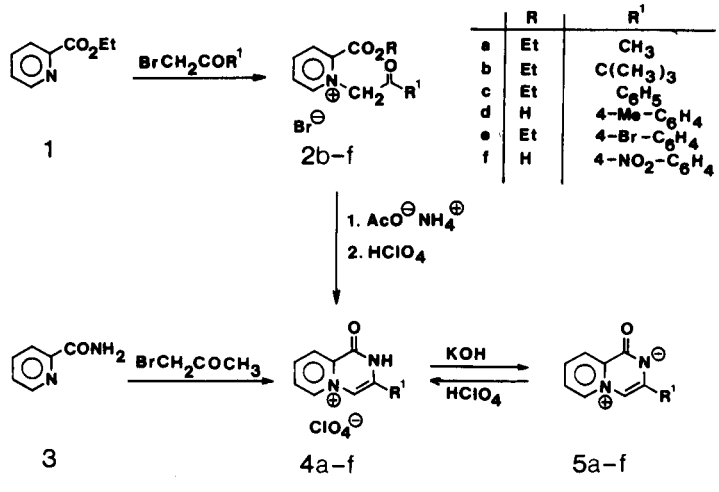
As a continuation of our work [2,3] concerning the synthesis and reactivity of pyrido[2,1-*f*]-*as*-triazinium-olates, we prepared now the related olates containing one N atom less, *i.e.* pyrido[1,2-*a*]pyrazinium-1- and 3-olates **5a-f** and **9** and pyrido[1,2-*b*]pyridazinium-4- and 2-olates **14**, **20**.

The first representative of pyrido[1,2-*a*]pyrazine system has been described by Schwab *et al.* [4]. This synthesis started from chelidonic acid and ethylenediamine and gave an 8*H*-1,8-dioxo-3,4-dihydro derivative. The use of pyrylium salt instead of chelidonic acid afforded 1(2*H*)-oxo-3,4-dihydropyridopyrazinium salt reported by Molina *et al.* [5]. The first fully aromatic 1-olate was described by Kröhnke *et al.* [6]. Later, Glover *et al.* [7] reported on the synthesis of the mesomeric betaine derived from 1,3-dioxopyridopyrazinium salt. Wittmann *et al.* [8] published the cycloaddition of a pyridinium-1-methylide and phenylisocyanate to give the first 3-olate derivative.

Among the derivatives of pyrido[1,2-*b*]pyridazine, the first olate (however in reduced form) was reported by Yamazaki *et al.* [9,10]. The fully aromatic pyrido[1,2-*b*]pyridazinium-4-olate was synthesized by Kakehi *et al.* [11]. Recently, Katritzky *et al.* [12] obtained 4-olate derivatives by ring transformation of 2-ethoxycarbonylpyrylium derivative with ketone hydrazones.

We prepared now quaternary pyridinium salts **2b-f** from ethyl 2-pyridinecarboxylate (**1**) and 2-bromoacetophenones or 1-bromopinacolone using the procedure developed by Kröhnke *et al.* [6] for the synthesis of 3-phenylpyrido[1,2-*a*]pyrazinium-1-olate (**5c**). In two cases, hydrolysis of the ester group also took place under the reaction conditions used to yield acid derivative **2d,f**. The ring closure effected by ammonium acetate resulted in easy formation of 3-substituted-1(2*H*)-oxopyridopyrazinium salts **4b-f** from ester **2d,c,e**, as well as from acids **2d,f**. The 3-methyl derivative **4a** was obtained in a different way by the reaction of picolinic acid amide (**3**) with 1-bromoacetone because the attempted quaternization of ethyl 2-pyridinecarboxylate (**1**) with 1-bromoacetone gave a multicomponent mixture. All the 1(2*H*)oxopyridopyrazinium salts **4a-f**, when reacted with base, readily gave the stable, zwitterionic pyrido[1,2-*a*]pyrazinium-1-olates **5a-f**.

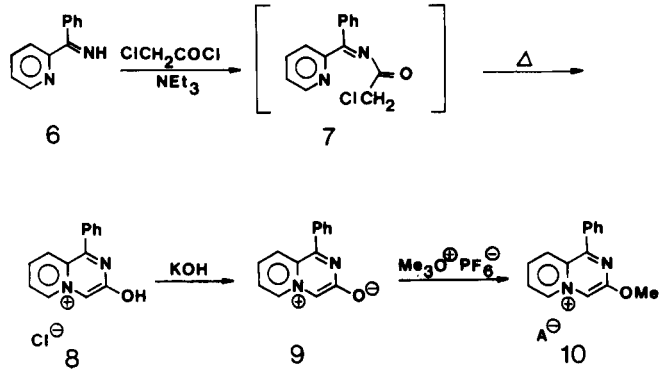
Scheme 1



New synthesis of 1-phenylpyrido[1,2-*a*]pyrazinium-3-olate (**9**) has been developed from phenyl-(2-pyridyl)ketimine (**6**) because the Wittmann method [8] led to *N*-substituted olates. The acylation of imine **6** with chloroacetyl chloride at 0° afforded the still open acylamide **7** which (without isolation and purification) was cyclised (in acetonitrile at reflux temperature) into 3-hydroxy-1-phenylpyrido[1,2-*a*]-pyrazinium chloride (**8**). Deprotonation of this hydroxy derivative **8** yielded the desired 3-olate **9**. Though compound **9** proved to be stable at room temperature, it decomposed, however, at elevated temperature [13].

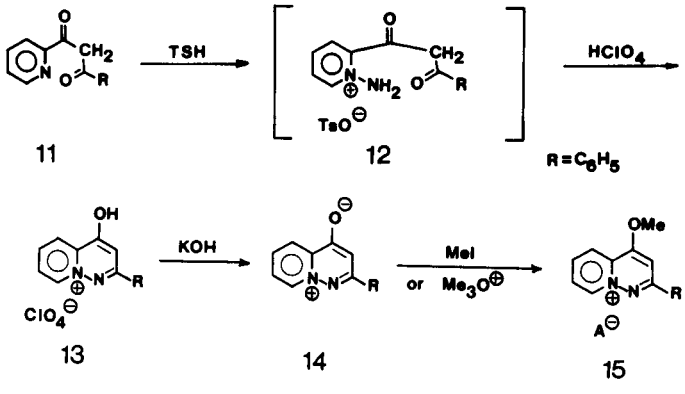
Derivatives of the other system, the pyrido[1,2-*b*]pyridazinium-olates **14**, **20** have been prepared by novel routes. Thus, when 1-phenyl-3-(2-pyridyl)-1,3-propanedione (**11**) [14] was *N*-aminated by *O*-tosylhydroxylamine (TSH) reagent [15], a spontaneous ring closure of the formed

Scheme 2



N-amino derivative took place, and 2-phenyl-4-hydroxypyrido[1,2-*b*]pyridazinium perchlorate (**13**) was isolated in 60% yield.

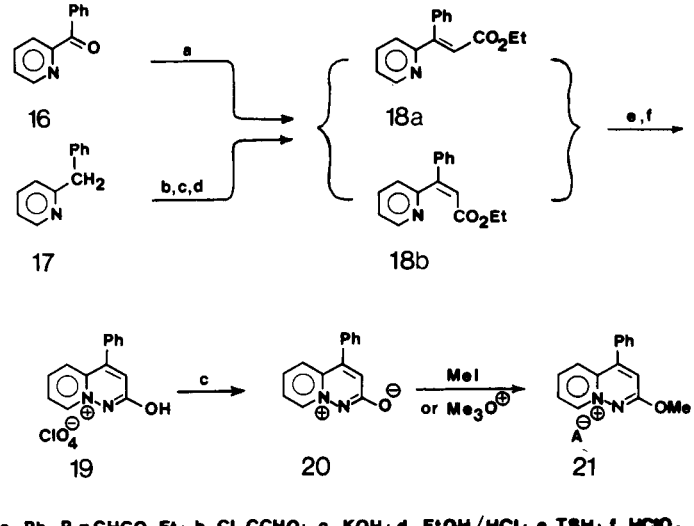
Scheme 3



The deprotonation of the 4-hydroxy derivative **13** by potassium hydroxide afforded the 4-olate derivative **14**.

The 2-olate **20** has been achieved *via* ethyl 3-phenyl-3-(2-pyridyl)acrylate (**18**). The synthesis of this ester **18** was

Scheme 4



a, $Ph_3P=CHCO_2Et$; b, Cl_3CCHO; c, KOH; d, EtOH/HCl; e, TSH; f, $HClO_4$

realised in two routes: (i) A modification of the method used by Tullock *et al.* [16] for the synthesis of 3-(2-pyridyl)-acrylic acid offered a possibility: condensation of 2-benzylpyridine (**17**) with chloral afforded an adduct which was hydrolysed by potassium hydroxide, and the formed acrylic acid was then esterified by ethanol. In this way, a mixture of the two isomeric acrylic esters **18a,b** was obtained in 40% overall yield. (ii) Starting from 2-benzoylpyridine (**16**) and using ethyl (triphenylphosphoranylidene)acetate as reagent, the Wittig reaction gave a mixture (1:1) of the two possible geometric isomers **18a** and **18b** in 80% yield.

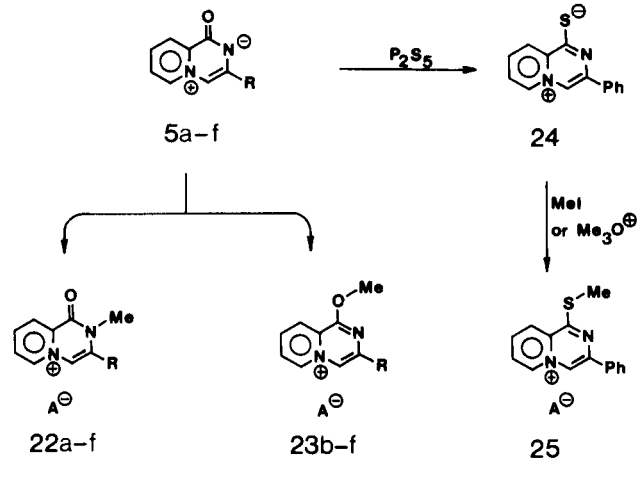
The mixture of isomers **18a,b** was reacted with TSH, and the resulting *N*-amino derivative was cyclised, without isolation, by perchloric acid to afford 4-phenyl-2-hydroxy derivative **19** in 30% yield. Deprotonation of this salt **19** by potassium hydroxide gave the aimed 2-olate **20**.

Protonation (*e.g.* by perchloric acid) of all the produced olate derivatives **5a-f**, **9**, **14** and **20** afforded the appropriate starting salts **4a-f**, **8**, **13**, **19** in almost quantitative yield.

Significant differences in products have been observed, however, with methylation reactions.

Thus, we have found that pyridopyrazinium-1-olates **5a-f** resulted in formation of NMe **22** and/or OMe **23** products in different ratios (determined by ^{1}H-nmr, see Experimental) depending on the soft or hard nature of the methylating agent used (Scheme 5 and Table I and III).

Scheme 5



When the methylation was carried out with the soft methyl iodide, 3-methyl-1-olate **5a** gave exclusively the NMe product **22a**. On the influence of the bulky 3-*t*-butyl group, the methylation of compound **5b** resulted in, however, predominant formation of OMe product **23b** and the ratio of that to NMe derivative **22b** was found to be 3:2. The 3-aryl-1-olates **5c-f** afforded mainly NMe compounds **22c-f** together with a small amount of OMe products **23c-f**; the proportion of this latter was found to increase

Table I

Methylation of Zwitterionic Pyrido[1,2-*a*]pyrazinium-1-olates **5a-f** and 1-thiolate **24**

Compound	R	Product A = I	Ratio	MP (°C)	Yield (%)	Product A = PF_6	Ratio	MP (°C)	Yield (%)
5a	CH_3	**22a**	100	233-236	80	[a]	-	-	-
5b	$C(CH_3)_3$	**22b + 23b**	40:60	260-265	90	**23b**	100	190-194	78
5c	C_6H_5	**22c + 23c**	92: 8	236-239	85	**22c + 23c**	48:52	220-224	100
5d	4-CH_3-C_6H_4	**22d + 23d**	86:14	274-280	97	**22d + 23d**	45:55	196-200	93
5e	4-Br-C_6H_4	**22e + 23e**	84:16	278-279	79	**22e + 23e**	36:64	228-232	91
5f	4-NO_2-C_6H_4	**22f + 23f**	72:28	300	85	**22f + 23f**	25:75	275-280	88
24	C_6H_5	**25**	100	305-306	97	**25**	100	268-272	97

[a] Olate **5a** formed a stable hydrate, therefore this reaction gave protonated salt **4a** contaminated with NMe product **22a** (A = PF_4).

Table II

Physical and Analytical Data of Quaternary Pyridinium Salts **2b-f** and of 1 (2*H*)-Oxopyrido[1,2-*a*]pyrazinium Salts **4b-f**

Product	R^1	Reaction time (h)	Yield (%)	MP (°C)	Product	Yield (%)	MP (°C)	Formula	Analyses (%) Calcd./Found C	H	N
2b	$C(CH_3)_3$	10	41	138-142	**4b**	65	245-248	$C_{12}H_{15}ClN_2O_5$	47.61	4.99	9.25
									47.42	5.24	9.57
2c	C_6H_5	2	78	173-175	**4c**	80	>300	$C_{14}H_{11}ClN_2O_5$	52.11	3.44	8.68
									52.34	3.61	8.43
2d	4-CH_3-C_6H_4	3.5	65	116-120	**4d**	61	305-308	$C_{15}H_{13}ClN_2O_5$	53.50	3.89	8.32
									53.49	4.05	8.28
2e	4-Br-C_6H_4	2	70	159-160	**4e**	69	293-295	$C_{14}H_{10}BrClN_2O_5$	41.87	2.51	6.98
									42.15	2.75	7.18
2f	4-NO_2-C_6H_4	9	52	235-237	**4f**	58	238-240	$C_{14}H_{10}ClN_3O_7$	45.73	2.74	11.43
									46.03	2.69	11.11

with electronwithdrawal *p*-substituents of the 3-aryl group. An interesting difference between the pyrazinium 1-olates **5a-f** and the analogous *as*-triazinium-4-olates [3] (containing one nitrogen more) can be observed: in methylation of these latter compounds with methyl iodide, formation of OMe products was not observed at all. This difference in reactivity can be probably explained by the π-electron-withdrawal behaviour of the nitrogen atom in *p*-position to the olate function. The availability of the lone pairs of electrons of the oxygen atom is decreased thereby in an electrophilic attack.

When the methylation was carried out with the hard, positively charged trimethyloxonium salt, the *t*-butyl derivative **5b** gave exclusively OMe compound **23**. In the case of 3-aryl derivatives **5c-f** both NMe **22c-f** and OMe compounds **23c-f** formed with predominance of the latter. The proportion of OMe derivatives was increased by enhanced electron-withdrawal property of the *p*-substituent of 3-aryl group [3].

The methylation of 3-phenyl-1-thiolate **24** with both methylating agents resulted in exclusive formation of SMe product **25**, in accordance with the expectations.

Pyrido[1,2-*a*]pyrazinium-3-olate (**9**, Scheme 2) proved to be rather unstable in reaction with methyl iodide at room temperature; a green, multicomponent mixture was produced which contained (according to the ^{1}H-nmr spectrum) only OMe product **10**. Attempts for isolation of this compound was unsuccessful. On the other hand, in the reaction of **9** with trimethyloxonium hexafluorophosphate, the OMe derivative (**10**, A = PF_6) was obtained in 40% yield.

The reaction of pyrido[1,2-*b*]pyridazinium-4- and 2-olates **14**, **20** (Schemes 3 and 4) resulted in the sole formation of OMe products **15** and **21** regardless of the soft or hard nature of the methylating reagent used. This fact supports our earlier assumption [2,3] that the nucleophilic reactivity of the nitrogen atom adjacent to the positively charged bridge-head nitrogen is strongly decreased. As a consequence of our earlier and present results concerning the alkylation of bicyclic bridge-head nitrogen containing zwitterionic olates, a selectivity rule can be proposed: *No methylation occurs on the nitrogen atom adjacent to the charged bridge-head N atom.*

To the best of our knowledge, methylation on this type

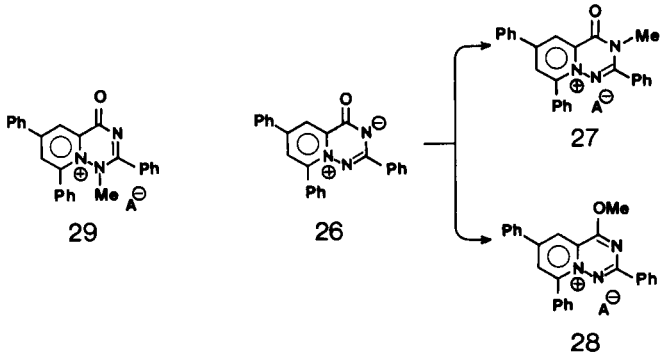
Table III

Analytical and Spectral Data of Methylated Pyrido[1,2-*a*]pyrazinium-1-olates **5a-f**

Compound (A = I)	^{1}H-NMR (ppm) (Trifluoroacetic acid) NCH_3	OCH_3	H-4	H-6	H-7	H-8	H-9	R	IR (cm^{-1}) (Potassium bromide)	Formula	Analyses (%) (Calcd./Found) C	H	N
22a	3.89	--	8.06	9.20	8.57	8.72	9.20	2.71	3040, 2910, 2900, 1660, 1610	$C_{10}H_{11}IN_2O$	39.76 39.67	3.67 3.96	9.27 9.38
22b + 23b	3.31	4.44	8.00	9.25	8.90 - 8.20			1.54	3070, 2980, 2950, 2860, 1620, 1570	$C_{13}H_{17}IN_2O$	45.36 45.58	4.98 5.16	8.14 7.89
22c + 23c	3.66	4.53	8.04	9.20	8.45	8.72	9.20	7.70	3070, 2930, 2850, 1680, 1640, 1620	$C_{15}H_{13}IN_2O$	49.47 49.78	3.60 3.84	7.69 7.62
22d + 23d	3.67	4.51	8.00	9.18	8.70	8.54	9.18	7.53 2.52	3040, 3020, 2920, 2860, 1680, 1640, 1620	$C_{16}H_{15}IN_2O$	50.81 51.06	4.00 4.22	7.41 7.43
22e + 23e	3.66	4.52	8.02	9.20	8.46	8.71	9.20	7.84 7.48	3030, 3010, 2930, 2850, 1670, 1640, 1610	$C_{15}H_{12}BrIN_2O$	40.66 40.69	2.75 2.71	6.32 6.28
22f + 23f	3.63	4.54	8.11	9.24	8.60	8.78	8.24	8.60 7.95	3060, 3030, 3020, 2980, 1680, 1650, 1620	$C_{15}H_{12}IN_3O_3$	44.03 44.30	2.96 3.16	10.28 9.98
(A = PF_6)													
23b	--	4.43	8.42	9.17	8.29	8.57	8.86	1.53	3100, 3060, 2960, 2920, 2860, 1620, 830	$C_{13}H_{17}F_6N_2OP$	43.10 43.37	4.73 4.49	7.73 7.62
22c + 23c	3.62	4.50	8.95 7.92	9.14	8.9 - 8.0		9.14	7.65	3130, 3080, 2960, 1670, 1640, 1620, 830	$C_{15}H_{13}F_6N_2OP$	47.13 47.19	3.43 3.52	7.33 6.97
22d + 23d	3.58	4.47		9.3 - 7.4					3110, 3080, 2920, 2850, 1680, 1630, 1610, 830	$C_{16}H_{15}F_6N_2OP$	48.49 48.79	3.82 4.14	7.07 7.22
22e + 23e	3.62	4.51	8.69	9.22	8.9 - 8.3		9.22	8.30 7.30	3100, 2950, 2920, 1680, 1640, 1620, 830	$C_{15}H_{12}BrF_6N_2OP$	39.07 39.30	2.62 2.79	6.08 5.99
22f + 23f	3.62	4.54	8.50	9.37	8.7 - 8.4		9.14	8.50 7.90	3130, 3080, 2950, 2920, 1630, 1600, 830	$C_{15}H_{12}F_6N_3O_3P$	42.17 42.07	2.83 3.08	9.84 9.59

of nitrogen of related bicyclic olate systems was published only in one case in the literature. Molina *et al.* [17] reported on the formation of 1-NMe product **29** in methylation of 2,6,8-triphenylpyrido[2,1-*f*]-*as*-triazinium-4-olate (**26**) with trimethyloxonium tetrafluoroborate.

Scheme 6



We repeated the synthesis of **26** according to the mentioned authors in a good yield; it was found, however, that methylation of **26** with trimethyloxonium tetrafluoroborate gave a mixture of 3-NMe **27** and OMe **28** (A = BF_4) products in a ratio of 48:52. The methylation with methyl iodide afforded exclusively 3-NMe derivative (**27**, A = I). Thus, formation of 1-NMe compound **29** was not observed at all in the reactions performed either by hard or by soft reagents. This experience is in accordance with the expectation of the proposed selectivity rule.

EXPERIMENTAL

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. The ir spectra were recorded with a Specord 75 IR apparatus and nmr spectra with a Varian EM 360-A spectrometer (TMS as internad standard).

3-Methyl-1(2*H*)-oxopyrido[1,2-*a*]pyrazinium Bromide Monohydrate (**4a**).

A suspension of **3** (12.2 g, 0.1 mole) in dry acetonitrile (50 ml) was refluxed with 1-bromoacetone (13.7 g, 8.4 ml, 0.1 mole) for 80 hours. The reaction mixture was cooled and filtered off. The crude product was recrystallized from acetonitrile-water to give colourless prisms (11.2 g, 43%), mp >300°; ir (potassium bromide): 3260, 3200, 3160, 3100, 3050, 2920, 2810, 1680, 1610, 1570, 1450 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 9.20 (m, 2H, H-6,9), 8.72 (t, 1H, H-8), 8.44 (t, 1H, H-7), 7.95 (s, 1H, H-4), 2.61 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_{11}BrN_2O_2$: C, 41.72; H, 4.28; N, 10.81. Found: C, 41.55; H, 3.99; N, 10.73.

3-Substituted-1(2*H*)-oxopyrido[1,2-*a*]pyrazinium Perchlorates **4b-f**.

General Procedure.

A solution of **1** (7.55 g, 50 mmoles) in acetonitrile (20 ml) was refluxed with the appropriate 2-bromoacetophenone derivative or 1-bromopinacolone (50 mmoles) for a period given in Table II. Ether (30 ml) was added to the reaction mixture, and the precipitated crystals were filtered off to give 1,2-disubstituted pyridinium salts **2b-f**.

A solution of the appropriate crude **2** (10 mmoles) in acetic acid (15 ml) was refluxed with ammonium acetate (5.0 g, 65 mmoles) for 2 hours. The reaction mixture was mixed with water (40 ml) and 70% perchloric acid (1.5 ml). The crystals were filtered and recrystallized from acetonitrile-ethyl acetate to give the product **4b-f** (Table II).

3-Methylpyrido[1,2-*a*]pyrazinium-1-olate Monohydrate (**5a**).

A suspension of **4a** (5.2 g, 20 mmoles) in ethanol (52 m) was stirred with potassium hydroxide (1.2 g, 20 mmoles) at room temperature for 20 minutes. Then the solution was mixed with chloroform (100 ml), filtered and concentrated. The residue was recrystallized from acetonitrile to give pale yellow prisms (2.4 g, 75%), mp 205-207°; ir (potassium bromide): 3080, 3020, 2980, 2920, 1590, 1550, 1510, 1450, 1390 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.84 (d, 1H, H-6), 8.46 (d, 1H, H-9), 8.05 (t, 1H, H-8), 7.9 (m, 1H, H-7), 7.72 (s, 1H, H-4), 3.29 (s, H_2O), 2.24 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 61.01; H, 5.92; N, 15.91.

3-(*t*-Butyl)pyrido[1,2-*a*]pyrazinium-1-olate (**5b**).

This compound was obtained from **3b** (6.05 g, 20 mmoles) using the previous procedure to give pale yellow needles (3.1 g, 74%), mp 214-216°; ir (potassium bromide): 3100, 2950, 2900, 2860, 1550, 1505, 1460, 1390 cm^{-1}; ^{1}H-nmr: (DMSO-d_6): δ 9.01 (d, 1H, H-6), 8.46 (1H, H-9), 8.0-7.9 (m, 2H, H-7,8), 7.88 (s, 1H, H-4), 1.52 (s, 9H, *t*-Butyl).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.93; H, 6.74; N, 13.59.

3-Arylpyrido[1,2-*a*]pyrazinium-1-olates **5c-f**.

General Procedure.

A suspension of the appropriate **4** (10 mmoles) in ethanol (50 ml) was stirred with a solution of sodium hydroxide (0.4 g, 10 mmoles) in water (2 ml) at room temperature for 1 hour. The reaction mixture was mixed with water (100 ml), and the precipitated crystals were filtered off and recrystallized from dimethylformamide to give the product **5c-f**.

3-Phenylpyrido[1,2-*a*]pyrazinium-1-olate (**5c**).

This compound was obtained from **4c** according to the general procedure, yellow needles (92%), mp 264-267° (lit [6] mp 252-255°).

3-(4-Methylphenyl)pyrido[1,2-*a*]pyrazinium-1-olate (**5d**).

This compound was obtained from **4d** according to the general procedure, yellow flakes (81%), mp 249-252°; ir (potassium bromide): 3080, 3040, 2910, 2840, 1560, 1500, 1460, 1410 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.92 (d, 1H, H-6), 8.50 (d, 1H, H-9), 8.44 (s, 1H, H-4), 8.09 (t, 1H, H-8), 8.00 (m, 1H, H-7), 7.99 (m, 2H, H-2',6'), 7.34 (m, 2H, H-3',5'), 2.40 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.42; H, 5.28; N, 11.63.

3-(4-Bromophenyl)pyrido[1,2-*a*]pyrazinium-1-olate (**5e**).

This compound was obtained from **4e** according to the general procedure, ochre-yellow flakes (70%), mp >310°; ir (potassium bromide): 3060, 1560, 1510, 1460, 1420 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.92 (d, 1H, H-6), 8.53 (d, 1H, H-9), 8.45 (s, 1H, H-4), 8.16-7.95 (m, 2H, H-7,8), 8.00 (m, 2H, H-2',6'), 7.66 (m, 2H, H-3',5').

Anal. Calcd. for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; N, 9.30. Found: C, 55.60; H, 3.27; N, 9.56.

3-(4-Nitrophenyl)pyrido[1,2-*a*]pyrazinium-1-olate (**5f**).

This compound was obtained from **4f** according to the general procedure, red flakes (74%), mp >310°; ir (potassium bromide): 3070, 3010, 1560, 1500, 1460, 1420, 1330 cm^{-1}; ^{1}H-nmr: because of the very poor solubility of **5f**, no nmr spectrum could be registered.

Anal. Calcd. for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.72. Found: C, 62.97; H, 3.54; N, 15.61.

3-Hydroxy-1-phenylpyrido[1,2-*a*]pyrazinium Chloride (**8**).

To a stirred solution of **6** (10.92 g, 60 mmoles) and triethylamine (6.06 g, 8.4 ml, 60 mmoles) in dry toluene (100 ml) was added dropwise a solution of chloroacetyl chloride (6.78 g, 4.8 ml, 60 mmoles) in dry toluene (20 ml) at -10°. Stirring was continued at −10° for 20 minutes and for an additional 20 minutes at room temperature. The precipitated crystals were filtered, washed with toluene (20 ml) and the mother liquor was concentrated. The residue was dissolved in dry acetonitrile (100 ml), and the solution was refluxed for 30 minutes. The reaction mixture was cooled, the crystals were filtered off and recrystallized from acetonitrile-water to give pale yellow needles (8.6 g, 55%), mp 199-201°; ir (potassium bromide): 3070, 3045, 2700-2500, 1630, 1550, 1480, 1460, 1445, 1405, 1370 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 9.24 (m, 1H, H-6), 8.83 (d, 1H, H-9), 8.69 (s, 1H, H-4), 8.30 (m, 2H, H-7,8), 7.82 (s, 5H, phenyl).

Anal. Calcd. for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83. Found: C, 64.93; H, 4.52; N, 10.60.

1-Phenylpyrido[1,2-*a*]pyrazinium-3-olate (**9**).

A suspension of **8** (5.2 g, 20 mmoles) in ethanol (52 ml) was stirred with a solution of potassium hydroxide (1.12 g, 20 mmoles) in water (4 ml) at room temperature for 10 minutes. Chloroform (100 ml) was added, the reaction mixture was filtered and concentrated. The residue was purified by column chromatography (alumina eluent:chloroform-methanol = 9:1). The second (orange) fraction was suspended in acetonitrile (10 ml) and filtered off to give orange prisms (3.1 g, 70%), mp 199-202°; ir (potassium bromide): 3040, 1580, 1530, 1500, 1380 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.50 (d, 1H, H-6), 7.74 (d, 1H, H-9), 7.7-7.3 (m, 7H, H-4,8 and phenyl), 7.14 (t, 1H, H-7).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.54; H, 4.80; N, 12.54.

3-Methoxy-1-phenylpyrido[1,2-*a*]pyrazinium Hexafluorophosphate (**10**, A = PF_6).

A suspension of **9** (0.22 g, 1 mmole) in dry dichloromethane (10 ml) was stirred with trimethyloxonium hexafluorophosphate (0.21 g, 1 mmole) at room temperature for 24 hours. The reaction mixture was mixed with ether, and the precipitated crystals were filtered off. The crude product (0.36 g, 95%) was recrystallized from acetonitrile-ether to give beige needles (0.17 g, 44%), mp 218-221°; ir (potassium bromide): 3110, 3030, 2950, 2840, 1620, 1540, 1490, 1470, 1390, 1340, 820 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 9.46 (d, 1H, H-6), 9.07 (s, 1H, H-4), 8.56 (d, 1H, H-9), 8.30 (m, 2H,

H-7,8), 7.9-7.6 (m, 5H, phenyl), 4.23 (s, 3H, OCH_3).

Anal. Calcd. for $C_{15}H_{13}F_6N_2PO$: C, 47.13; H, 3.43; N, 7.33. Found: C, 47.32; H, 3.75; N, 7.32.

4-Hydroxy-2-phenylpyrido[1,2-*b*]pyridazinium Perchlorate (**13**).

To a stirred solution of ethyl *O*-tosylacetohydroxamate (6.8 g, 26.4 mmoles) in dioxane (40 ml) 70% perchloric acid (3.6 ml) was added dropwise at 15° and stirring was continued for 15 minutes. Then **11** (4.5 g, 20 mmoles) was added to the solution, and a solution of ammonium acetate (2.92 g, 38 mmoles) in water (12 ml) was dropped at 15°. The reaction mixture was stirred at room temperature for 3 hours then it was mixed with water (100 ml) and extracted with nitromethane (3 × 20 ml). The extract was concentrated and the residue was recrystallized from acetonitrile-ethyl acetate to give colourless needles (3.9 g, 60%), mp 247-248°; ir (potassium bromide): 3100, 3080, 2650-2400, 1595, 1580, 1520, 1460, 1390, 1340, 1100 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 9.41 (dd, 1H, H-8), 8.78 (dd, 1H, H-5), 8.53 (t, 1H, H-6), 8.28 (t, 1H, H-7), 8.08 (m, 2H, H-2',6'), 7.64 (s, 1H, H-3), 7.6 (m, 3H, H-3',4',5').

Anal. Calcd. for $C_{14}H_{11}ClN_2O_4$: C, 52.11; H, 3.44; N, 8.68. Found: C, 52.38; H, 3.63; N, 8.84.

2-Phenylpyrido[1,2-*b*]pyridazinium-4-olate (**14**).

A suspension of **13** (3.7 g, 11.2 mmoles) in ethanol (74 ml) was stirred with a 11% solution of potassium hydroxide in water (6 ml) at room temperature for 10 minutes. Chloroform (150 ml) was added to the reaction mixture, then filtered and concentrated. The residue was recrystallized from acetonitrile to give pale yellow prisms (1.6 g, 63%); mp 193-194°; ir (potassium bromide): 3110, 3060, 3050, 1630, 1580, 1490, 1450, 1420 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 9.06 (d, 1H, H-5), 8.58 (d, 1H, H-8), 8.06-7.88 (m, 2H, H-6,7), 8.00 (m, 2H, H-2',6'), 7.5 (m, 3H, H-3',4',5'), 6.65 (s, 1H, H-3).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.72; H, 4.68; N, 12.39.

4-Methoxy-2-phenylpyrido[1,2-*b*]pyridazinium Iodide (**15**, A = I).

A suspension of **14** (0.22 g, 1 mmole) in acetonitrile (10 ml) was refluxed with methyl iodide (1.14 g, 0.5 ml, 8 mmoles) for 35 hours. The reaction mixture was concentrated to half of its volume and was mixed with ethyl acetate (5 ml). The precipitated crystals were filtered off, and the crude product (0.26 g, 72%) was recrystallized from acetonitrile-ethyl acetate to give yellow prisms (0.22 g, 60%), mp 154-155°; ir (potassium bromide): 3090, 3030, 2900, 2830, 1600, 1510, 1460, 1440, 1420 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 9.46 (d, 1H, H-8), 9.00-8.40 (m, 3H, H-5,6,7), 8.30 (m, 3H, H-3,2',6'), 7.75 (m, 3H, H-3',4',5'), 4.49 (s, 3H, OCH_3).

Anal. Calcd. for $C_{15}H_{13}IN_2O$: C, 49.47; H, 3.60; N, 7.69. Found: C, 49.63; H, 3.88; N, 7.65.

4-Methoxy-2-phenylpyrido[1,2-*b*]pyridazinium Hexafluorophosphate (**15**, A = PF_6).

A solution of **14** (0.22 g, 1 mmole) in dry dichloromethane (10 ml) was stirred with trimethyloxonium hexafluorophosphate (0.21 g, 1 mmole) at room temperature for 24 hours. The reaction mixture was mixed with ether (10 ml) and the precipitate was filtered off. The crude product (0.35 g, 92%) was recrystallized from acetonitrile-ethyl acetate to give colourless crystals (0.21 g, 55%), mp 203-206°; ir (potassium bromide); 3110, 3000, 2910, 2850, 1605, 1510, 1460, 1420, 830 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 9.63 (d, 1H, H-8), 8.66 (m, 2H, H-5,6), 8.33 (m, 3H, H-7,2',6'), 8.09 (s, 1H, H-3), 7.66 (m, 3H, H-3',4',5'), 4.39 (s, 3H, OCH_3).

Anal. Calcd. for $C_{15}H_{13}F_6N_2PO$: C, 47.13; H, 3.42; N, 7.33. Found: C, 47.38; H, 3.61; N, 7.08.

Ethyl 3-Phenyl-3-(2-pyridyl)acrylate **18a,b**.

Procedure A.

A solution of 2-benzoylpyridine **16** (9.15 g, 50 mmoles) in dry toluene (100 ml) was refluxed with ethyl (triphenylphosphoranylidene)acetate (18 g, 51 mmoles) for 60 hours. The solution was concentrated to dryness, and the residue was mixed with ether (20 ml) and petroleum ether (40 ml). The crystals were filtered, washed with petroleum ether, and the mother liquor was evaporated to dryness. The residue was distilled *in vacuo* to give a pale yellow oil (10.3 g, 81%), bp 120-130° (0.01 torr); ir (liquid film): 3030, 2970, 2900, 1695, 1605, 1570, 1550, 1260, 1140 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.67 (dd, 1H, H-6'), 7.9-7.2 (m, 7.5H, H-2,3',4' and phenyl), 7.03 (t, 1H, H-5'), 6.45 (s, 0.5H, H-2), 4.02 (q, 2H, CH_2), 1.02 (t, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.65; H, 6.23; N, 5.30.

Procedure B.

A mixture of 2-benzylpyridine **17** (4.3 g, 4.1 ml, 25 mmoles) and chloral (5 g, 3.3 ml, 34 mmoles) was heated at 100° for 3 hours, then after addition of further amount of chloral (5 g) for another 3 hours. The reaction mixture was cooled, mixed with water (30 ml) and extracted with chloroform (3 × 15 ml), then purified by column chromatography (silica gel, eluted by chloroform). The first fraction was recrystallized from petroleum ether to give colourless needles (5.8 g, 72%), mp 97-100°. This adduct (4.7 g, 15 mmoles) was added in small portions to the stirred and boiling solution of potassium hydroxide (5.0 g, 90 mmoles) in ethnaol (20 ml). Boiling was continued for 1 hour, then the reaction mixture was cooled, filtered and washed with ethanol. The mother liquor was evaporated to dryness and the residue was refluxed in ethanol (50 ml) saturated with hydrochloric acid for 15 hours. The reaction mixture was diluted with water, neutralized by sodium carbonate, and extracted with chloroform (3 × 10 ml). The extract was concentrated and the residue was distilled *in vacuo* to give pale yellow oil (2.1 g, 56%), bp 120-130° (0.01 torr). This compound was identical with the product obtained in procedure A.

2-Hydroxy-4-phenylpyrido[1,2-*b*]pyridazinium Perchlorate (**19**).

To a solution of a mixture (1:1) of **18a,b** (7.6 g, 30 mmoles) in dichloromethane (20 ml) was added a solution of TSH (5.7 g, 30 mmoles) in dichloromethane. The reaction mixture was stirred at room temperature for 3 hours, then was mixed with 70% perchloric acid (10 ml) and stirred for 5 hours. After being evaporated to dryness, the residue was treated with water (30 ml) and extracted with nitromethane (3 × 15 ml). The extract was concentrated, the residue was triturated with ethyl acetate, and the precipitated crystals were filtered off and recrystallized from acetonitrile-water to give colourless prisms (2.9 g, 30%), mp 235-238°; ir (potassium bromide): 3200, 3080, 3040, 2600-2300, 1610, 1490, 1430, 1400, 1100 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 9.23 (d, 1H, H-8), 8.40 (m, 2H, H-5,6), 8.19 (t, 1H, H-7), 7.70 (s, 5H, phenyl), 7.59 (s, 1H, H-2).

Anal. Calcd. for $C_{14}H_{11}ClN_2O_5$: C, 52.11; H, 3.44; N, 8.68. Found: C, 52.21; H, 3.48; N, 8.61.

4-Phenylpyrido[1,2-*b*]pyridazinium-2-olate (**20**).

A suspension of **19** (1.61 g, 5 mmoles) in ethanol (10 ml) was stirred with a solution of potassium hydroxide (0.31 g, 5.5 mmoles) in water (0.5 ml) at room temperature for 5 minutes. Chloroform (30 ml) was added to the reaction mixture, then was filtered and concentrated. The residue was recrystallized from acetonitrile to give colourless prisms (0.67 g, 60%), mp 212-213°; ir (potassium bromide): 3060, 3010, 1610, 1540, 1405, 1390 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.74 (d, 1H, H-8), 7.80-7.30 (m, 8H, H-5,6,7 and phenyl), 6.99 (s, 1H, H-3).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.87; H, 4.88; N, 12.58.

2-Methoxy-4-phenylpyrido[1,2-*b*]pyridazinium Iodide (**21**, A = I).

A suspension of **20** (0.22 g, 1 mmole) in dry acetonitrile (5 ml) was refluxed with methyl iodide (1.14 g, 0.5 ml, 8 mmoles) for 3 hours. Ether (20 ml) was added and the crystals were filtered and recrystallized from acetonitrile to give yellow needles (0.27 g, 73%), mp 161-163°; ir (potassium bromide): 3100, 2990, 2930, 2830, 1600, 1470, 1430, 1420, 1370 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 9.36 (d, 1H, H-8), 8.45 (m, 2H, H-5,6), 8.27 (t, 1H, H-7), 7.72 (s, 5H, phenyl), 7.57 (s, 1H, H-3), 4.37 (s, 3H, OCH_3).

Anal. Calcd. for $C_{15}H_{13}IN_2O$: C, 49.47; H, 3.60; N, 7.69. Found: C, 49.30; H, 3.69; N, 7.72.

2-Methoxy-4-phenylpyrido[1,2-*b*]pyridazinium Hexafluorophosphate (**21**, A = PF_6).

A solution of **20** (0.22 g, 1 mmole) in dry dichloromethane (10 ml) was stirred with trimethyloxonium hexafluorophosphate (0.21 g, 1 mmole) at room temperature for 24 hours. Then ether was added, the crystals were filtered off and recrystallized from acetonitrile to give colourless needles (0.22 g, 58%), mp 184-195°; ir (potassium bromide): 3060, 3020, 2910, 2830, 1600, 1480, 1430, 1380, 820 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 9.33 (d, 1H, H-8), 8.41 (m, 2H, H-5,6), 8.14 (t, 1H, H-7), 7.69 (s, 5H, phenyl), 7.52 (s, 1H, H-3), 4.37 (s, 3H, OCH_3).

Anal. Calcd. for $C_{15}H_{13}F_6N_2PO$: C, 47.13; H, 3.43; N, 7.33. Found: C, 47.07; H, 3.76; N, 7.05.

Methylation of 3-Substituted Pyrido[1,2-*a*]pyrazinium-1-olates **5a-f** with Methyl Iodide.

General Procedure.

A suspension of the appropriate **5a-f** (1 mmole) in dimethylformamide (5 ml) was stirred with methyl iodide (2.28 g, 1 ml, 16 mmoles) at room temperature for 5 hours [a]. The reaction mixture was mixed with ether (15 ml), and the crystals were filtered off to give a mixture of 3-substituted-2-methyl-1(2*H*)-oxopyrido-[1,2-*a*]pyrazinium iodide **22a-f** (A = I) and 3-substituted-1-methoxypyrido[1,2-*a*]pyrazinium iodides **23a-f** (A = I). The product was analysed without purification (Tables I and III). [a] In the case of compound **5f**, stirring was continued for 3 days.

Methylation of 3-Substituted Pyrido[1,2-*a*]pyrazinium-1-olates **5a-f** with Trimethyloxonium Hexafluorophosphate.

General Procedure.

A suspension of the appropriate **5a-f** (1 mmole) in dry dichloromethane (10 ml) was stirred with trimethyloxonium hexafluorophosphate (0.21 g, 1 mmole) at room temperature for 24 hours. Then ether (20 ml) was added, and the crystals were filtered off to give a mixture of **22a-f** (A = PF_6) and **23a-f** (A = PF_6) [a]. The product was analysed without further purification (Tables I and III). [a] The olate **5a** formed a stable hydrate therefore its reaction with trimethyloxonium hexafluorophosphate afforded protonated hexafluorophosphate salt **4** which contained a small proportion of N-methylated product **22a** (A = PF_6).

3-Phenylpyrido[1,2-*a*]pyrazinium-1-thiolate (**24**).

A stirred mixture of **5c** (4.44 g, 20 mmoles) and phosphorous pentasulfide (6.66 g, 30 mmoles) was heated in dry pyridine (100 ml) at 100° for 2 hours. The excess of pyridine was evaporated *in vacuo*, the residue was mixed with water (200 ml) and stirred at room temperature for 30 minutes. The precipitated crystals were filtered off and recrystallized from acetonitrile-dimethylformamide to give ochre-yellow needles (3.4 g, 71%), mp 215-218°; ir (potassium bromide): 3090, 3070, 3020, 1630, 1610, 1590, 1530, 1460 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 9.46 (d, 1H, H-9), 9.00 (d, 1H, H-6), 8.74 (s, 1H, H-4), 8.15-7.91 (m, 2H, H-7,8), 8.12 (m, 2H, H-2',6'), 7.45 (m, 3H, H-3',4',5').

Anal. Calcd. for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.76. Found: C, 70.29; H, 4.35; N, 11.73.

1-Methylthio-3-phenylpyrido[1,2-*a*]pyrazinium Iodide (**25**, A = I).

A suspension of **24** (0.24 g, 1 mmole) in dimethylformamide (5 ml) was stirred with methyl iodide (1.14 g, 0.5 ml, 8 mmoles) at room temperature for 2 hours. Then ether (10 ml) was added to the reaction mixture, and the crystals were filtered off to give analytically pure yellow needles (0.37 g, 97%), mp 305-306°; ir (potassium bromide): 3060, 3030, 2970, 2920, 2890, 1630, 1540, 1480, 1440, 1380 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 9.20 (d, 1H, H-6), 9.00 (s, 1H, H-4), 8.69 (m, 2H, H-8,9), 8.30 (m, 3H, H-7,2',6'), 7.61 (m, 3H, H-3',4',5'), 2.97 (s, 3H, SCH_3).

Anal. Calcd. for $C_{15}H_{13}IN_2S$: C, 47.38; H, 3.45; N, 7.37. Found: C, 47.15; H, 3.62; N, 7.42.

1-Methylthio-3-phenylpyrido[1,2-*a*]pyrazinium Hexafluorophosphate (**25**, A = PF_6).

A suspension of **24** (0.24 g, 1 mmole) in dry dichloromethane (5 ml) was stirred with trimethyloxonium hexafluorophosphate (0.21 g, 1 mmole) at room temperature for 20 hours. The reaction mixture was mixed with ether (15 ml) and the crystals were filtered off to give analytically pure pale yellow prisms (0.39 g, 97%), mp 268-272°; ir (potassium bromide): 3120, 3080, 2930, 2850, 1630, 1550, 1490, 1445, 1380, 830 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid-deuterioacetonitrile): δ 9.23 (d, 1H, H-6), 9.02 (s, 1H, H-4), 8.65 (m, 2H, H-8,9), 8.30 (m, 3H, H-7,2',6'), 7.63 (m, 3H, H-3',4',5'), 2.98 (s, 3H, SCH_3).

Anal. Calcd. for $C_{15}H_{13}F_6N_2PS$: C, 45.23; H, 3.29; N, 7.03. Found: C, 45.52; H, 3.41; N, 6.89.

3-Methyl-2,6,8-triphenyl-4(3*H*)oxopyrido[2,1-*f*]-*as*-triazinium Iodide (**27**, A = I).

A suspension of **26** (0.38 g, 1 mmole) in a mixture of acetonitrile (5 ml) and dimethylformamide (5 ml) was refluxed with methyl iodide (1.37 g, 0.6 ml, 9 mmoles) for 3 hours. Then ether (20 ml) was added to the reaction mixture, and the crystals were filtered off. The crude product (0.5 g, 97%) was recrystallized from acetonitrile-ethyl acetate to give ochre-yellow needles (0.37 g, 72%), mp 249-250°; ir (potassium bromide): 3030, 3020, 2870, 1710, 1610, 1590, 1550, 1420, 1380 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 9.32 (d, 1H, H-5), 8.68 (d, 1H, H-7), 7.68 (m, 15H, phenyl), 3.77 (s, 3H, NCH_3).

Anal. Calcd. for $C_{16}H_{20}IN_3O$: C, 60.36; H, 3.90; N, 8.12. Found: C, 60.14; H, 4.06; N, 8.23.

Methylation of 2,6,8-Triphenylpyrido[2,1-*f*]-*as*-triazinium-4-olate (**26**) with Trimethyloxonium Tetrafluoroborate.

A suspension of **26** (0.38 g, 1 mmole) in dry dichloromethane (10 ml) was stirred with trimethyloxonium tetrafluoroborate (0.15 g, 1 mmole) at room temperature for 20 hours. The reaction mixture was mixed with ether (25 ml), and the precipitated crystals were filtered off to give a mixture (0.46 g, 96%) of 3-methyl-2,6,8-triphenyl-4(3*H*)-oxopyrido[2,1-*f*]-*as*-triazinium tetrafluoroborate (**27**, A = BF_4) and 4-methoxy-2,6,8-triphenylpyrido[2,1-*f*]-*as*-triazinium tetrafluoroborate (**28**, A = BF_4), mp 270-280°; ir (potassium bromide): 3060, 2910, 2850, 1705, 1610, 1595, 1580, 1500, 1480, 1390, 1370, 1080 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.93 (dd, 1H, H-5), 8.53 and 8.36 (two doublets, 1H, H-7; ratio 1:1), 8.3-7.4 (m, 15H, phenyl), 4.57 and 3.46 (two singlets; 3H, OMe and NMe; ratio 52:48).

Anal. Calcd. for $C_{26}H_{20}BF_4N_3O$: C, 65.43; H, 4.22; N, 8.80. Found: C, 65.64; H, 4.38; N, 8.73.

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