2-Methylpyridinium Salts as 1,4-Dinucleophiles. IV. Westphal Condensation with 2-Alkyl-1-aminoazinium Substrates

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Condensation of 2-alkyl-1-aminopyridinium, quinolinium or 1-alkyl-2-aminoisoquinolinium salts with 1,2-acenaphthenequinone or 9,10-phenanthrenequinone in the presence of base, gave pyrido[1,2-*b*]pyridazinium salts in good yields.

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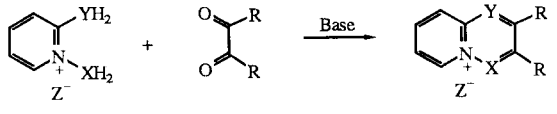
The Westphal condensation [1,2] (Figure 1) is one of the easiest ways to produce a quinolizinium cation **3**, (X = CCOR', Y = CR") by means of a base catalyzed condensation between 2-alkylpyridinium **1** and 1,2-dicarbonyl derivatives.



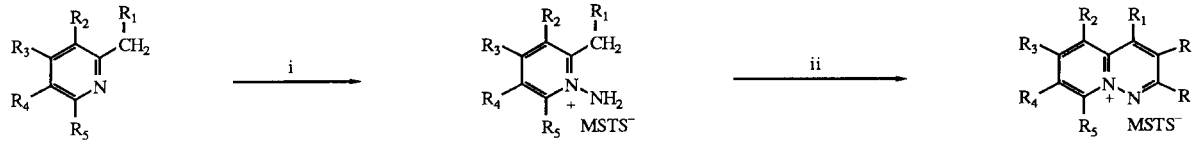
1 2 3

Figure 1

Most of the work published on the process has been performed with 1,2-dialkylazinium salts producing quinolizinium derivatives [3-7]. However, Baranova *et al* [8] described the use of 1,2-diaminopyridinium salts **1** (X = Y = N), as N-N substrates, generating diazaquinolizinium derivatives.

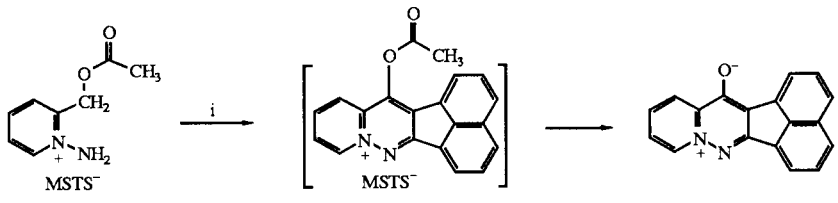
In the present paper we report our results using N-C substrates **1**, (X = N, Y = CR", Figure 1) in order to generate a pyridazinium moiety fused with the azine precursor. So starting with 2-alkyl-1-aminopyridinium salts **5**, pyrido[1,2-*b*]pyridazinium salts **6** should be easily obtained. The preparation of the starting 1-aminoazinium salts **5** was performed by direct amination of the available azine (Figure 2).

As it is shown in Table 1, two already described methods were used: one (method A) was amination with *O*-hydroxylaminosulfonic acid [9], which produced good yields only in examples **5a-c**. The other one [10], using *O*-hydroxylaminomesitylenesulfonate produced high yields with most of the examples. Then, compounds **5** were condensed with the corresponding 1,2-dicarbonyls (Figure 2), either 1,2-acenaphthenequinone or 9,10-phenanthrenequinone, using sodium acetate as base in refluxing acetone. Other dicarbonyl compounds were also tested, as benzil, diacetyl, *etc.* being always recovered at the end of the process in more than 80% yield, without traces of the condensation product. All results are shown in Table 2. As it can be seen there, melting points of all compounds were higher than 250-270° and they were not determined. One example not represented in Table 2 is the 2-acetoxymethyl derivative **5h**, which with 1,2-acenaphthenequinone produced the heterobetaine **6n** by simultaneous hydrolysis of the ester group (Figure 3).



4 5 6

Figure 2. Reagents: i) *O*-Hydroxylaminomesitylensulfonate/CH_2Cl_2, rt. ii) Sodium acetate/1,2-dicarbonyl compounds/Acetone, reflux.



5h 6n

Figure 3. Reagents: i) Sodium acetate/acenapthenequinone/Acetone, reflux.

Table 1

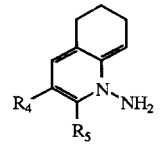
N-Aminoazinium Salts **5**

Compound	R^1	R^2	R^3	R^4	R^5	X	Method [a]	Reaction time, minutes	Yield (%)	Mp (°C)
5a	H	H	H	H	H	I	A	45	80	150-152 [b]
5b	H	H	H	H	CH_3	I	A	360	40	182-185 [b]
5c	H	H	CH_3	H	H	I	A	360	50	109-110 [b]
5d	H	H	CH_3	H	CH_3	MSTS [d]	B	10	80	185-188
5e	$-(CH_2)_3-$		H	H	H	MSTS	B	10	64	92-94
5f	$-(CH_2)_3-$		H	$-(CH_2)_3-$		MSTS	B	10	82	201-204
5g	C_6H_5	H	H	H	H	MSTS	B	10	83	133-134
5h	$OCOCH_3$	H	H	H	H	MSTS	B	10	53	129-131
5i	H	H	H	$-(CH=CH)_2-$		MSTS	B	20	65	195-197 [c]
5j	H	$-(CH=CH)_2-$		H	H	MSTS	B	10	58	172-173 [c]
5k	*p*-ClC_6H_4	$-(CH=CH)_2-$		H	H	MSTS	B	10	77	195-197

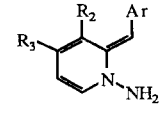
[a] Method A, performed with *O*-hydroxylaminosulfonic acid [9]. Method B was performed with *O*-hydroxylaminomesitylenesulfonate [10]. [b] Described in [9]. [c] Described in [10]. [d] MSTS = Mesitylenesulfonate.

Related pyrido[1,2-*b*]pyridazinium-1-olates have been previously reported in the literature. Initially, Ning *et al.* [11] prepared benzo[*b*] derivates by pyrolysis of 2,1-benzisoxazoles, Kakehi and coworkers [12] obtained the parent heterocyclic system as a secondary product in a photochemical process. Katritzky *et al.* [13] described a more general method, preparing several derivatives from pyrilium salts.

From all the **5** substrates, the reaction failed with the cyclic derivatives **5e** and **5f** as well as the 1-(4-chlorophenyl)-isoquinolinium salt **5k**, probably due to the high stability of the corresponding anhydrobases **7e**, **7f** and **7k** which act as intermediates (Figure 4). However, the benzyl derivative **5g**, producing a similar anhydrobase **7g**, reacted with good yields. Opposite results were previously obtained with the analogous C-C substrates [4].



7e, R_4, R_5 = H
7f, R_4, R_5 = $(-CH_2-)_3$



7g, R_2, R_3 = H Ar = C_6H_5
7k, R_2–R_3 = $(-CH=CH-)_2$ Ar = *p*-ClC_6H_4

Figure 4

The analytical data of all new products are listed in Table 3. The ^{1}H-nmr data of compounds **6** show two downfield signals. One, from the 6-H, in the *alpha* position with respect to the bridgehead nitrogen atom appears *ca.* δ = 9.5 pm. The other one, from the 1-H appears at about 9.3 ppm. As it could be expected, the heterobetaine **6n** shows a less deshielded 6-H position (*ca.* 0.45 ppm) due to delocalization of the negative charge of the olate group. The proton resonances for the anion mesitylenesulfonate are not included in Table 3, as they are independent of the heterocyclic cation. In all cases signals appear at 6.62 ppm for the aromatic protons and, 2.44 and 2.15 ppm for the *ortho* and *para* methyl groups, respectively.

Table 2

Pyrido[1,2-*b*]pyridazinium Salts **6**

Compound	R R	R^1	R^2	R^3	R^4	R^5	X	Reaction time, hours	Yield (%)	Mp (°C)
6a	NPDL [a]	H	H	H	H	H	I	4	60	>270 [d]
6b	DPDL [b]	H	H	H	H	H	I	4	55	>250 [d]
6c	NPDL	H	H	CH_3	H	H	I	3	65	>270 [c]
6d	DPDL	H	H	CH_3	H	H	I	3	70	>250 [d]
6e	NPDL	H	H	H	H	CH_3	I	3	80	>270 [d]
6f	DPDL	H	H	H	H	CH_3	I	3	70	>250 [d]
6g	NPDL	H	H	CH_3	H	CH_3	MSTS [c]	1.5	65	>250 [f]
6h	DPDL	H	H	CH_3	H	CH_3	MSTS	1.5	67	>250 [f]
6i	NPDL	Ph	H	H	H	H	MSTS	0.5	44	242-244 [f]
6j	DPDL	Ph	H	H	H	H	MSTS	1.5	81	>250 [f]
6k	NPDL	H	H	H	$-(CH=CH)_2-$		MSTS	22	30	>250 [g]
6l	DPDL	H	H	H	$-(CH=CH)_2-$		MSTS	22	42	>250 [g]
6m	NPDL	H	$-(CH=CH)_2-$		H	H	MSTS	1	88	>250 [f]

[a] NPDL: Naphth-1,8-di–yl. [b] DPDL: Diphenyl-*o*,*o'*-di-yl. [c] MSTS: Mesitylenesulfonate. [d] From methanol. [e] From ethanol. [f] From ethanol/ethyl acetate. [g] From methanol/ethyl acetate.

As a conclusion, the method seems to be a simple and efficient way to produce pyrido[1,2-*b*]pyridazinium salts; however, the process seems to be limited to the use of *ortho*-quinones as dielectrophiles. Studies are in progress to extend the method to other dicarbonyl reagents, and to other heterocyclic systems.

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 700 or 1310 spectrophotometers. The ^{1}H-nmr spectra were obtained on a Varian FT-80 instrument, using DMSO-d_6 as the deuterated solvent and TMS as the internal reference. The analyses are described for the new compounds.

Preparation of 2-Alkyl-1-aminoazinium Salts, General Procedure (Table 1, Figure 2, Compounds **5a-k**).

The derivates **5a-c** were prepared using *O*-hydroxylaminosulfonic acid as described in [9]. The **5d-k** products were obtained as follows:

To a stirred solution of *O*-hydroxylaminomesitylenesulfonate (10 mmoles, 2.15 g) in dichloromethane (20 ml), the corresponding azine (10 mmoles) in dichloromethane (20 ml) was added dropwise. The mixture was stirred at room temperature for the time described in Table 1. Diethyl ether was then added (30 ml) to precipitate the *N*-aminoazinium salt **5** which was triturated with ether (3 × 5 ml).

Preparation of Pyrido[1,2-*b*]pyridazinium Salts. General procedure (Table 2, Figure 2, Compounds **6a-m**).

1-Aminoazinium salt **5** (2 mmoles), the corresponding *o*-qui-

Table 3

New *N*-Aminoazinium Salts **5** and Pyrido[1,2-*b*]pyridazinium Salts **6** Prepared

Compound	Molecular Formulae	Requirred (%) Found (%) [a] C	H	N	IR (υ max)	^{1}HNM Data (δ)
5d	$C_{17}H_{24}N_2SO_3$	60.80 60.68	7.41 7.18	8.37 8.32	3272, 1637	7.60 (s, 2H), 6.96 (s, 2H, NH_2), 2.67 (s, 6H), 2.45 (s, 3H)
5e	$C_{18}H_{24}N_2SO_3.1/2H_2O$	60.78 60.47	7.08 6.76	7.83 7.43	3220, 1604	7.13-8.68 (m, 5H, NH_2), 2.77-3.03 (m, 4H), 1.79-2.05 (m, 4H)
5f	$C_{22}H_{30}N_2SO_3$	65.48 65.63	7.59 7.51	6.87 6.96	3217, 1639	7.78 (s, 1H), 6.96 (bs, 2H, NH_2), 2.77-3.00 (m, 8H), 1.70-1.77 (m, 8H)
5g	$C_{21}H_{24}N_2SO_3$	65.53 65.59	6.33 6.29	7.16 7.28	3200, 1654	7.24-8.78 (m, 11H, NH_2), 4.38 (s, 2H)
5h	$C_{17}H_{22}N_2SO_5$	55.74 55.71	6.19 6.05	7.78 7.64	3217, 1639	8.01-8.88 (m, 6H, NH_2), 5.44 (s, 2H), 2.19 (s, 3H)
5k	$C_{25}H_{25}ClN_2SO_3$	64.02 63.91	5.37 5.25	5.97 6.12	3287, 1648	7.35-8.63 (m, 12H, NH_2), 4.92 (s, 2H)
6a	$C_{18}H_{11}N_2I$	56.61 56.69	3.30 2.91	6.63 6.35	1625, 1421	9.75 (d, J = 6.6 Hz, 1H), 9.51 (s, 1H), 7.98-8.72 (m, 9H)
6b	$C_{19}H_{13}N_2I.H_2O$	56.29 56.47	3.33 3.55	6.65 6.59	1628, 1374	10.28 (s, 1H), 9.83 (d, J = 6.5 Hz, 1H), 9.08 (d, J = 7.4 Hz, 1H), 8.37-8.91 (m, 6H), 7.75-7.90 (m, 4H)
6c	$C_{19}H_{13}N_2I.3/2H_2O$	54.30 54.43	3.59 3.20	6.80 6.63	1638, 1449	9.58 (d, J = 6.9 Hz, 1H), 9.21 (s, 1H), 7.85-8.52 (m, 8H), 2.79 (s, 3H)
6d	$C_{21}H_{15}N_2I$	59.61 59.86	3.78 3.58	6.96 6.65	1638, 1375	10.04 (s, 1H), 8.68 (d, J = 6.1 Hz, 1H) 7.80-8.29 (m, 10H), 2.82 (s, 3H)
6e	$C_{19}H_{13}N_2I.1/2H_2O$	56.09 56.43	3.48 3.24	6.95 6.93	1625, 1492	9.44 (s, 1H), 7.98-8.66 (m, 9H), 3.15 (s, 3H)
6f	$C_{21}H_{15}N_2I$	59.58 59.85	3.68 3.58	6.54 6.64	1629, 1401	10.33 (s, 1H), 7.86-9.23 (m, 11H), 3.18 (s, 3H)
6g	$C_{29}H_{26}N_2SO_3.2/3H_2O$	70.28 70.41	5.45 5.30	5.30 5.66	1664, 1512	9.25 (s, 1H), 7.96-8.58 (m, 8H), 3.07, 2.70 (2s, 6H)
6h	$C_{31}H_{28}N_2SO_3.H_2O$	70.74 70.69	5.76 5.45	5.37 5.32	1638, 1376	9.70 (s, 1H), 7.60-8.48 (m, 10H), 2.94, 2.74 (2s, 6H)
6i	$C_{33}H_{26}N_2SO_3$	74.56 74.69	4.72 4.94	4.90 5.28	1620, 1424	9.91 (d, J = 6.3 Hz, 1H), 7.72-8.68 (m, 14H)
6j	$C_{35}H_{28}N_2SO_3.H_2O$	71.85 72.01	5.03 4.91	4.53 4.80	1623, 1447	9.13 (d, J = 7.4 Hz, 1H), 8.50-8.75 (m, 3H), 7.25-8.05 (m, 13H)
6k	$C_{31}H_{24}N_2SO_3.H_2O$	71.40 71.24	4.87 4.62	5.09 5.36	1606, 1441	9.50 (s, 1H), 9.30 (d, J = 7.3 Hz, 1H), 7.91-8.94 (m, 11H)
6l	$C_{33}H_{26}N_2SO_3$	70.78 70.44	4.51 4.67	5.08 5.28	1600, 1371	10.16 (s, 1H), 9.38 (d, J = 7.2 Hz, 1H), 7.75-9.12 (m, 13H)
6m	$C_{31}H_{24}N_2SO_3.H_2O$	71.24 71.06	4.62 4.78	5.36 5.55	1605, 1438	10.66 (s, 1H), 9.25-9.45 (m, 3H), 8.04-8.84 (m, 9H)
6n	$C_{18}H_{10}N_2O.3/4H_2O$	71.29 71.63	3.49 3.34	8.95 9.28	1637, 1513	9.31 (d, J = 6.2 Hz, 1H), 8.81 (d, J = 7.4 Hz, 1H), 7.77-8.35 (m, 8H)

none (2 mmoles) and anhydrous sodium acetate (2 mmoles) were suspended in acetone (5 ml). The mixture was refluxed as indicated in Table 2. The warm solution was filtered, and the solid was washed with acetone (3 × 5 ml). Crystallization as described in Table 2 yielded the corresponding compounds **6** analytically pure. The acenaphtho[1,2-*b*]pyrido[1,2-*b*]pyridazinium-13-olate **6n** was prepared using the above described procedure (30% yield, 3 hours, mp >250°).

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