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NEW ACRIDIZINIUM SALTS DERIVED FROM [2-(BROMOMETHYL)PHENYL]CARBONYL COMPOUNDS

L. M. Potikha[1]*, V. V. Sypchenko[1], and V. A. Kovtunenko[1]

A new method is proposed for the preparation of 1-hydroxypyrido[1,2-b]isoquinolinium bromides by intramolecular aromatic electrophilic substitution in 3-hydroxy-1-(2-formylbenzyl)pyridinium, 3-hydroxy- and 3-amino-1-[2-(4-chlorobenzoyl)benzyl]pyridinium bromides. The alkylation of pyridine and some of its derivatives by 2-(bromomethyl)benzaldehyde, 2-(bromomethyl)benzophenone derivatives, and methyl 2-(bromomethyl)benzoate was studied.

Keywords: 2-(bromomethyl)benzaldehyde, 2-(bromomethyl)benzophenone, methyl 2-(bromomethyl)-benzoate, pyrido[1,2-*b*]isoquinoline, aromatic electrophilic substitution, cyclization.

Pyrido[1,2-*b*]isoquinolinium (acridizinium) salts are capable of Diels–Alder cycloadditions and are used in the synthesis of a range of biologically active compounds. These salts have been used in the preparation of drugs for the treatment of neurodegenerative conditions, neurotoxic injuries, and AIDS [1-3]. The high photochemical activity of these salts accounts for their use as efficient fluorescence probes in biological [4] and chemical studies [5]. Many workers have been actively developing methods for the synthesis of acridizinium salts following their discovery by Bradsher [6]. With a single exception, all these methods are based on the addition of the isoquinoline fragment to 2-carbonyl-, 2-cyano-, and 2-benzylpyridine derivatives, as proposed by Bradsher [7, 8]. The fusion of a pyridine ring to an isoquinoline fragment has been used to prepare only a single compound, namely, 3-hydroxypyrido[1,2-*b*]isoquinolinium salt [1, 2]. Each of these routes has its limitations due to the cyclization reaction mechanism or difficulties in obtaining 2-substituted pyridines. In the present work, still another method is proposed for the preparation of pyrido[1,2-*b*]isoquinolinium salts using pyridine and its readily available derivatives.

γ-Halocarbonyl compounds as 1,4-dielectrophilic reagents are convenient building blocks for the preparation of various heterocyclic systems, including isoquinoline systems. In previous work [9, 10], we showed that condensed isoquinolines are readily formed by the cyclization of quaternary 1,3-diazolium salts using 2-(bromomethyl)benzaldehyde (**1a**), 2-(bromomethyl)benzophenone derivatives **1b**,**c**, and methyl 2-(bromo-methyl)benzoate (**1d**). In the present work, we studied the reaction of bromomethyl derivatives **1a**-**d** with pyridine (**2d**) and some of pyridine derivatives **2a**-**c**,**e**-**h**, yielding new pyridinium salts **3a**-**m**, which are potential precursors for the proposed synthesis of new pyrido[1,2-*b*]isoquinoline derivatives.

*To whom correspondence should be addressed, e-mail: potikha_l@mail.ru.

[1]Kyiv Taras Shevchenko National University, 64 Volodymirska St., Kyiv 01033, Ukraine.

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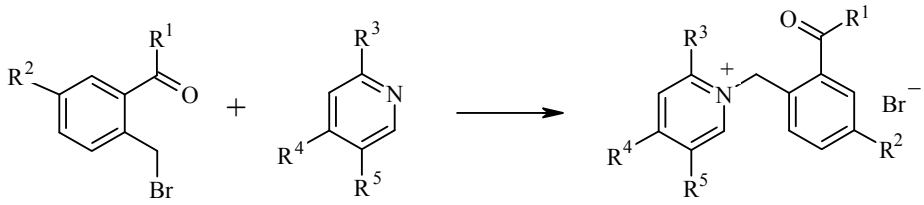
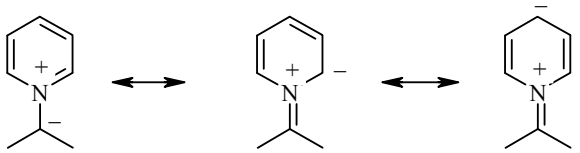


1a–d **2a–h** **3a–m**

Starting compounds	Product	R^1	R^2	R^3	R^4	R^5
1a, **2a**	**3a**	H	H	H	H	OH
1a, **2b**	**3b**	H	H	Me	H	OH
1b, **2a**	**3c**	4-ClC_6H_4	H	H	H	OH
1b, **2b**	**3d**	4-ClC_6H_4	H	Me	H	OH
1b, **2c**	**3e**	4-ClC_6H_4	H	H	H	NH_2
1a, **2d**	**3f**	H	H	H	H	H
1b, **2d**	**3g**	4-ClC_6H_4	H	H	H	H
1b, **2e**	**3h**	4-ClC_6H_4	H	H	H	Me
1b, **2f**	**3i**	4-ClC_6H_4	H	H	H	Br
1a, **2g**	**3j**	H	H	H	NH_2	H
1b, **2h**	**3k**	4-ClC_6H_4	H	H	NMe_2	H
1c, **2c**	**3l**	Ph	NO_2	H	H	NH_2
1d, **2a**	**3m**	OMe	H	H	H	OH

We discovered that maintaining γ-halocarbonyl compounds **1a-d** in benzene or acetone with pyridines **2a-h** led to the formation of quaternary pyridinium salts **3a-m** in 58-91% yields. Products **3a-f**,**h-l** were obtained at room temperature, while the preparation of salts **3g**,**m** required heating (see Experimental). Salts **3** dissolved readily in water, but were only moderately soluble in methanol and ethanol. The physicochemical and spectral characteristics of these new salts **3a-m** are given in Tables 1 and 2.

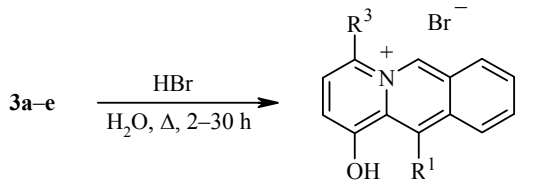
It is known [11] that upon the action of base, quaternary pyridinium salts are capable of forming pyridinium ylides, which are commonly used in chemical synthesis. These ylides are usually represented as a set of resonance structures **A**, **B**, and **C**.



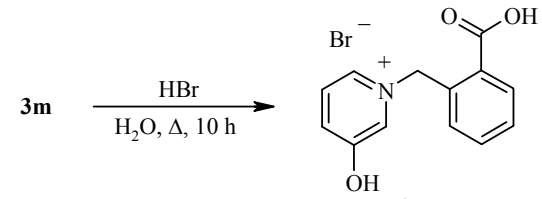
A **B** **C**

In our case, the addition of NaOH or Et_3N to solutions of salts **3** resulted in a darker color, but attempts to isolate and characterize the transformation products of these salts were unsuccessful, and heating these salts for 3-10 h led to complex mixtures of unidentified compounds. At the same time, heating solutions of salts **3a-e** in 48% hydrobromic acid at reflux gave their cyclization products, namely, 1-hydroxypyrido[1,2-*b*]isoquinolinium bromides **4a-d.**

The structure of bromides **4a-d** was established on the basis of their spectral and analytical data (Tables 1 and 2). A characteristic feature of the ^{1}H NMR spectra of these salts was the presence of a low-field one-proton singlet for H-6 (> 10 ppm). The presence of the 4-chlorophenyl substituent at position 11 in salts **4c**,**d** led to an upfield shift of the hydroxyl proton and H-10 proton signals by 0.6-1.0 ppm relative to the analogous proton signals of unsubstituted salts **4a**,**b**. The observed shift was evidently a consequence of shielding by the benzene ring, which was perpendicular to the plane of the tricyclic pyrido[1,2-*b*]isoquinoline system.



4a–d



3n

4 a $R^1 = R^3 = H$; **b** $R^1 = H$, $R^3 = Me$; **c** $R^1 = 4\text{-}ClC_6H_4$, $R^3 = H$; **d** $R^1 = 4\text{-}ClC_6H_4$, $R^3 = Me$

The yield of cyclization products **4a-d** depended on the structure of the starting pyridinium salt **3**. Thus, the yields of bromides **4a**,**b** from formyl derivatives **3a**,**b** were higher than for bromides **4c**,**d** from the corresponding benzoyl derivatives **3c**,**d**. The yields of products **4a**,**c** from salts **3a**,**c**, which were unsubstituted at position 2 in the pyridine ring, were higher than for products **4b**,**d** from the corresponding 2-methyl derivatives **3b**,**d**. The amino-substituted salt **3e** cyclized much more readily than its hydroxy-substituted analog **3c**. The cyclization of salt **3e** was accompanied by hydrolysis, thus the same product **4c** was obtained in 68% and 10% yields, respectively, from both salts **3e**,**c**. These results might have been expected in light of the data of Matsuda et al. [12] on the transformations of structurally similar 8-aminoquinolizinium salts. The observed dependence of the yield of cyclic products on the structure of the starting pyridinium salts was due to the cyclization reaction mechanism involving electrophilic aromatic substitution in the pyridine ring with participation of the salt **3** carbonyl group activated in acidic medium.

A similar type of transformation has been used for the preparation of 8-aminoquinolizinium salts [12] involving cyclization of 3-aminopyridinium *N*-allylylides derived from alkyl but-2-enoate derivatives in an acidic medium. The back-donated 1,6-cyclization mechanism, in the opinion of these authors, entails participation of the pyridinium ylide resonance form **B**. Factors stabilizing this resonance form should clearly favor such a mechanism. In a study of a similar cyclization reaction of *N*-allyl-1,3-diazolium ylides obtained from dypnone derivatives (generated from the corresponding *N*-allyl-1,3-diazolium salts) [13], we found an increase in reaction rate and yield of cyclization products (azolo[*a*]pyridines) with stronger electron-withdrawing properties of the 1,3-diazole substituents.

In order to check the probability of the ylide mechanism for the cyclization of salts **3a-e**, we studied the behavior of salts **3f-k** with different substituents at different positions of the pyridine ring under various conditions. Mixtures of unidentified products were obtained in basic medium under standard conditions for the formation of ylides [11]. The desired acridizinium salts also did not form in acidic medium, regardless of the acidity of the medium and reaction temperature. Similarly, an attempt to cyclize the salt **3l** also failed, while only the hydrolysis product, acid **3n**, was obtained in the case of 3-hydroxy-1-[2-(methoxycarbonyl)-benzyl]pyridinium bromide (**3m**).

Thus, the presence of strong electron-donating substituents at the *meta* position of the pyridine ring in the starting pyridinium salt **3**, as well as an acidic medium were necessary for the formation of acridizinium salts **4**. Cyclization was also facilitated by the presence of other electron-donor substituents in the pyridine ring and enhanced carbonyl activity of the substituent in the *N*-benzyl fragment. These findings, in our view, unequivocally indicate an electrophilic aromatic substitution mechanism for the cyclization of salts **3a-e**.

TABLE 1. Physicochemical Characteristics of Compounds **3-6**

Compound	Empirical formula	Found, % / Calculated, %					Mp*, °C	Yield, %
		C	H	Br	Cl	N		
3a	$C_{13}H_{12}BrNO_2$	53.10 / 53.08	4.15 / 4.11	27.14 / 27.16	—	4.73 / 4.76	170-171	86
3b	$C_{14}H_{14}BrNO_2$	54.53 / 54.56	4.55 / 4.58	25.96 / 25.93	—	4.56 / 4.55	201-202	74
3c	$C_{19}H_{15}BrClNO_2$	56.42 / 56.39	3.75 / 3.74	19.72 / 19.74	8.80 / 8.76	3.45 / 3.46	226-227	90
3d	$C_{20}H_{17}BrClNO_2$	57.40 / 57.37	4.11 / 4.09	19.04 / 19.08	8.48 / 8.47	3.39 / 3.35	199-200	69
3e	$C_{19}H_{16}BrClN_2O$	56.50 / 56.53	3.97 / 3.99	19.81 / 19.79	8.75 / 8.78	6.92 / 6.94	188-189	91
3f	$C_{13}H_{12}BrNO$	56.13 / 56.14	4.37 / 4.35	28.75 / 28.73	—	5.05 / 5.08	181-182	89
3g	$C_{19}H_{15}BrClNO$	58.70 / 58.71	3.91 / 3.89	20.58 / 20.56	9.10 / 9.12	3.59 / 3.60	203-205	87
3h	$C_{20}H_{17}BrClNO$	59.67 / 59.65	4.23 / 4.25	19.83 / 19.84	8.82 / 8.80	3.50 / 3.48	204-205	88
3i	$C_{19}H_{14}Br_2ClNO$	48.80 / 48.81	3.05 / 3.02	34.20 / 34.18	7.60 / 7.58	3.02 / 3.00	190-191	71
3j	$C_{13}H_{13}BrN_2O$	53.30 / 53.26	4.50 / 4.47	27.30 / 27.26	—	9.55 / 9.56	176-177	91
3k	$C_{21}H_{20}BrClN_2O$	58.40 / 58.42	4.65 / 4.67	18.55 / 18.51	8.20 / 8.21	6.45 / 6.49	195-196	87
3l	$C_{19}H_{16}BrN_3O_3$	55.11 / 55.09	3.91 / 3.89	19.32 / 19.29	—	10.13 / 10.14	168-169	58
3m	$C_{14}H_{14}BrNO_3$	51.84 / 51.87	4.36 / 4.35	24.62 / 24.65	—	4.35 / 4.32	196-198	60
3n	$C_{13}H_{12}BrNO_3$	50.30 / 50.34	3.91 / 3.90	25.79 / 25.76	—	4.51 / 4.52	211-213	55
4a	$C_{13}H_{10}BrNO$	56.56 / 56.55	3.67 / 3.65	28.93 / 28.94	—	5.06 / 5.07	> 235 (decomp.)	69
4b	$C_{14}H_{12}BrNO$	57.98 / 57.95	4.19 / 4.17	27.53 / 27.54	—	4.85 / 4.83	> 250 (decomp.)	74
4c	$C_{19}H_{13}BrClNO$	59.07 / 59.02	3.41 / 3.39	20.65 / 20.66	9.18 / 9.17	3.64 / 3.62	> 300	10 (68)*[2]
4d	$C_{20}H_{15}BrClNO$	59.98 / 59.95	3.80 / 3.77	19.96 / 19.94	8.88 / 8.85	3.48 / 3.50	> 300	38
5	$C_{19}H_{12}ClNO$	74.66 / 74.64	3.97 / 3.96	—	11.63 / 11.60	4.57 / 4.58	> 235 (decomp.)	72
6	$C_{21}H_{15}BrClNO_2$	58.85 / 58.83	3.57 / 3.53	18.66 / 18.64	8.23 / 8.27	3.26 / 3.27	> 260 (decomp.)	64

*Recrystallization solvents: $MeNO_2$ (compounds **3a-e**,**h-n**), 1:1 mixture of 2-propanol–*n*-hexane (compounds **3f**,**g**), methanol (compounds **4a-d**), 2-propanol (compounds **5** and **6**).

*[2]The yield in the cyclization of salt **3e**.

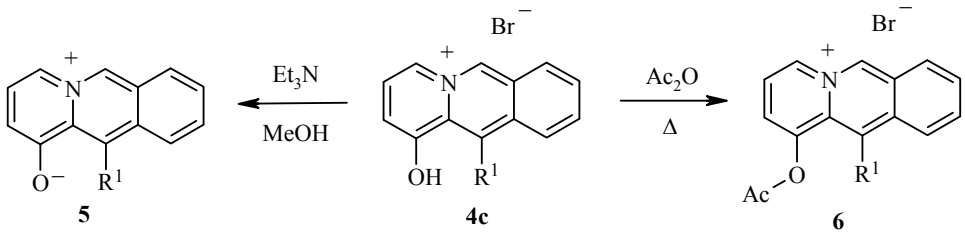
The chemical properties of 1-hydroxyacridizinium salts have hardly been examined. Only Earley et al. [1, 2] noted a cycloaddition reaction of 1-hydroxypyrido[1,2-*b*]isoquinolinium perchlorate, which was obtained by hydrolysis of the corresponding 1-methoxy derivative. Jones [8] has reported that structurally similar 1(3)-hydroxyquinolizinium derivatives exhibited acidic properties and yielded deprotonated (betaine) forms upon reaction with bases. The reaction of 11-aryl-1-hydroxyacridizinium bromide **4c** with Et_3N at room temperature also lead to the betaine **5**, which was indicated by the lack of an OH signal in ^1H NMR spectra and upfield shift of all the signals for the protons of the tricyclic fragment. We should also note the upfield position of the signal for the H-2 proton (at 6.33 ppm) due to the effect of the anionic site in this molecule. The IR spectrum of betaine **5** lacked a hydroxy group band, while a band was found at 1597 cm^{-1} characteristic for the olate C–O bond [14].

TABLE 2. Spectral Characteristics of Compounds **3-6**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
1	2	3
3a	3054, 2909, 1693 (C=O), 1579, 1509, 1310, 1194 (C-O), 1145, 758, 680	11.90 (1H, br. s, OH); 10.15 (1H, s, CHO); 8.60-8.59 (2H, m, H-2,6); 8.14-8.11 (1H, m, H-3'); 8.04 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-4); 7.97 (1H, dd, ^3J = 8.0, ^3J = 6.0, H-5); 7.77-7.74 (2H, m, H-4',5'); 7.40 (1H, m, H-6'); 6.19 (2H, s, CH_2)
3b	3054, 2863, 1695 (C=O), 1579, 1525, 1473, 1442, 1305 (C-O), 1150, 856, 758, 740	11.58 (1H, br. s, OH); 10.17 (1H, s, CHO); 8.37 (1H, d, ^4J = 2.8, H-6); 8.18-8.16 (1H, m, H-3'); 8.03 (1H, dd, ^3J =8.5, ^4J = 2.8, H-4); 7.98 (1H, d, ^3J = 8.5, H-3); 7.72-7.71 (2H, m, H-4',5'); 6.83-6.82 (1H, m, H-6'); 6.17 (2H, s, CH_2); 2.60 (3H, s, CH_3)
3c	3012, 2904, 2848, 1646 (C=O), 1589, 1514, 1315, 1269 (C-O), 1155, 1088, 923, 742	11.91 (1H, br. s, OH); 8.61-8.59 (2H, m, H-2,6); 7.98 (1H, dd, ^3J = 8.5, ^4J = 1.5, H-4); 7.95 (1H, dd, ^3J = 8.8, ^3J = 5.0, H-5); 7.74 (2H, d, ^3J = 8.5, H-2",6"); 7.70 (1H, td, ^3J = 8.0, ^4J =1.6, H-5'); 7.63-7.57 (3H, m, H-4',3",5"); 7.54 (1H, dd, ^4J = 1.6, ^3J = 8.0, H-3'); 7.51 (1H, d, ^3J = 8.0, H-6'); 5.94 (2H, s, CH_2)
3d	3432, 3018, 2900, 1659 (C=O), 1584, 1530, 1315, 1269 (C-O), 930, 742	11.60 (1H, br. s, OH); 8.35 (1H, d, ^4J = 2.7, H-6); 7.93 (1H, dd, ^3J =8.5, ^4J = 2.7, H-4); 7.89 (1H, d, ^3J = 8.5, H-3); 7.75 (2H, d, ^3J = 8.5, H-2",6"); 7.66 (1H, m, H-5'); 7.63-7.57 (4H, m, H-3',4',3",5"); 7.11 (1H, d, ^3J = 8.0, H-6'); 5.92 (2H, s, CH_2); 2.59 (3H, s, CH_3)
3e	3421 (NH_2), 3251 (NH_2), 3132, 1659 (C=O), 1584, 1509, 1269, 1088, 941, 745	8.13 (1H, d, ^3J = 6.0, H-6); 8.04-8.03 (1H, m, H-2); 7.74-7.70 (3H, m, H-4,2",6"); 7.65 (1H, dd, ^3J = 8.5, ^3J = 6.0, H-5); 7.63-7.59 (3H, m, H-5',3",5"); 7.58-7.50 (3H, m, H-3',4',6'); 6.67 (2H, br. s, NH_2); 5.80 (2H, s, CH_2)
3f	3049, 1693 (C=O), 1625, 1579, 1476, 1300, 1194, 1158, 786, 770, 755, 685	10.13 (1H, s, CHO); 9.09 (2H, d, ^3J = 6.0, H-2,6); 8.66 (1H, t, ^3J = 8.0, H-4); 8.19 (2H, dd, ^3J = 6.0, ^3J = 8.0, H-3,5); 8.14-8.13 (1H, m, H-3'); 7.78-7.77 (2H, m, H-4',5'); 7.42-7.41 (1H, m, H-6'); 6.25 (2H, s, CH_2)
3g	3042, 2969, 1647 (C=O), 1589, 1488, 1309, 1267, 1085, 929, 783, 738, 688, 657	9.07 (2H, d, ^3J = 6.0, H-2,6); 8.63 (1H, t, ^3J = 8.0, H-4); 8.17 (2H, dd, ^3J = 6.0, ^3J = 8.0, H-3,5); 7.75-7.73 (3H, m, H-5',2",6"); 7.66-7.58 (4H, m, H-3',4',3",5"); 7.52 (1H, d, ^3J = 8.0, H-6'); 6.09 (2H, s, CH_2)
3h	3002, 1656 (C=O), 1584, 1266, 1086, 933, 747, 662	9.04 (1H, s, H-2); 8.93 (1H, d, ^3J = 6.0, H-6); 8.47 (1H, d, ^3J = 8.0, H-4); 8.06 (1H, dd, ^3J = 8.0, ^3J = 6.0, H-5); 7.75 (2H, d, ^3J = 8.5, H-2",6"); 7.72 (1H, t, ^3J = 8.0, H-5'); 7.63-7.58 (3H, m, H-4',3",5"); 7.55-7.52 (2H, m, H-3',6'); 5.98 (2H, s, CH_2); 2.51 (3H, s, CH_3)
3i	3028, 1654 (C=O), 1584, 1266, 1085, 928, 750, 739, 659	9.59 (1H, s, H-2); 9.14 (1H, d, ^3J = 6.0, H-6); 8.92 (1H, d, ^3J = 8.0, H-4); 8.15 (1H, dd, ^3J = 8.0, ^3J = 6.0, H-5); 7.77 (2H, d, ^3J = 8.5, H-2",6"); 7.70 (1H, t, ^3J = 8.0, H-5'); 7.64-7.54 (5H, m, H-3',4',6',3",5"); 6.03 (2H, s, CH_2)
3j	3354 (NH_2), 3158 (NH_2), 1700 (C=O), 1654, 1543, 1207, 1171, 835	10.16 (1H, s, CHO); 8.25 (2H, br. s, NH_2); 8.19 (2H, d, ^3J = 6.8, H-2,6); 8.07 (1H, d, ^3J = 7.2, H-3'); 7.70-7.68 (2H, m, H-4',5'); 7.25 (1H, d, ^3J = 7.2, H-6'); 6.90 (2H, d, ^3J = 6.8, H-3,5); 5.79 (2H, s, CH_2)
3k	3452, 3380, 3007, 1649 (C=O), 1571, 1266, 1171, 931, 840, 744	8.27 (2H, d, ^3J = 7.5, H-2,6); 7.71 (2H, d, ^3J = 8.5, H-2",6"); 7.65 (1H, t, ^3J = 8.0, H-5'); 7.60 (2H, d, ^3J = 8.5, H-3",5"); 7.52 (1H, t, ^3J = 8.0, H-4'); 7.49 (1H, d, ^3J = 8.0, H-3'); 7.37 (1H, d, ^3J = 8.0, H-6'); 7.00 (2H, d, ^3J = 7.5, H-3,5); 5.56 (2H, s, CH_2), 3.19 (6H, s, $N(CH_3)_2$)

TABLE 2 (continued)

1	2	3
3l	3287 (NH_2), 3132 (NH_2), 1669 (C=O), 1581, 1525, 1501 (NO_2), 1354 (NO_2), 1300, 1261, 723, 649	8.49 (1H, dd, ^3J = 8.5, ^4J = 2.5, H-5'); 8.26 (1H, d, ^4J = 2.5, H-3'); 8.18 (1H, d, ^3J = 6.0, H-6); 8.13-8.12 (1H, m, H-2); 7.78 (2H, d, ^3J = 8.0, H-2",6"); 7.77-7.73 (2H, m, H-4,4"); 7.67 (1H, dd, ^3J = 8.5, ^3J = 6.0, H-5); 7.62-7.55 (3H, m, H-6',3",5"); 6.71-6.70 (2H, br. s, NH_2); 5.96 (2H, s, CH_2)
3m	3140 (OH), 2894, 1718 (C=O), 1579, 1506, 1486, 1437, 1308 (C-O), 1277 (C-O), 1142 (C-O), 1088, 807, 736, 685	11.79 (1H, br. s, OH); 8.59-8.57 (2H, m, H-2,6); 8.07 (1H, dd, ^3J = 8.0, ^4J = 1.6, H-3'); 8.02 (1H, d, ^3J = 8.0, H-4); 7.95 (1H, dd, ^3J = 8.5, ^3J = 6.0, H-5); 7.70 (1H, td, ^3J = 8.0, ^4J = 1.2, H-5'); 7.59 (1H, td, ^3J = 8.0, ^4J = 1.2, H-4'); 7.47 (1H, d, ^3J = 8.0, H-6'); 6.14 (2H, s, CH_2); 3.88 (3H, s, OCH_3)
3n	3442 (OH), 3039, 2946, 1718 (C=O), 1579, 1509, 1484, 1207 (C-O), 1155 (C-O), 1067, 770, 737, 680, 647	11.75 (1H, br. s, OH); 8.60-8.58 (2H, m, H-2,6); 8.06 (1H, d, ^3J = 8.0, H-3'); 8.02 (1H, br. d, ^3J = 8.0, H-4); 7.94 (1H, dd, ^3J = 8.0, ^3J = 6.0, H-5); 7.64 (1H, t, ^3J = 8.0, H-5'); 7.55 (1H, t, ^3J = 8.0, H-4'); 7.47 (1H, d, ^3J = 8.0, H-6'); 6.17 (2H, s, CH_2)
4a	3437 (OH), 3292, 1638, 1563, 1396, 1318 (C-O), 910, 760, 724	12.40 (1H, br. s, OH); 10.64 (1H, s, H-6); 9.29 (1H, s, H-11); 8.95 (1H, d, ^3J = 7.5, H-4); 8.46 (1H, d, ^3J = 8.0, H-10); 8.42 (1H, d, ^3J = 8.0, H-7); 8.05 (1H, t, ^3J = 8.0, H-9); 7.96 (1H, t, ^3J = 8.0, H-8); 7.80 (1H, t, ^3J = 7.5, H-3); 7.36 (1H, d, ^3J = 7.5, H-2)
4b	—	12.28 (1H, br. s, OH); 10.28 (1H, s, H-6); 9.41 (1H, s, H-11); 8.67 (1H, d, ^3J = 8.0, H-7); 8.50 (1H, d, ^3J = 8.0, H-10); 8.09 (1H, t, ^3J = 8.0, H-9); 8.00 (1H, t, ^3J = 8.0, H-8); 7.78 (1H, d, ^3J = 8.0, H-3); 7.32 (1H, d, ^3J = 8.0, H-2); 3.00 (3H, s, CH_3)
4c	3431 (OH), 3023, 2961, 1535, 1385, 1297 (C-O), 1155, 1088, 783, 729	11.76 (1H, br. s, OH); 10.72 (1H, s, H-6); 9.00 (1H, d, ^3J = 6.5, H-4); 8.47 (1H, d, ^3J = 7.5, H-7); 7.97-7.95 (2H, m, H-8,9); 7.81 (1H, t, ^3J = 8.0, H-3); 7.60 (2H, d, ^3J = 8.0, H-2',6'); 7.49 (1H, d, ^3J = 8.0, H-10); 7.42 (2H, d, ^3J = 8.0, H-3',5'); 7.19 (1H, d, ^3J = 8.0, H-2)
4d	3421 (OH), 2863, 1561, 1383, 1349, 1145 (C-O), 1083, 801, 791, 750	11.60 (1H, br. s, OH); 10.39 (1H, s, H-6); 8.80 (1H, d, ^3J = 8.0, H-7); 7.99-7.97 (2H, m, H-8,9); 7.82 (1H, d, ^3J = 8.0, H-3); 7.60 (2H, d, ^3J = 8.0, H-2',6'); 7.51 (1H, d, ^3J = 8.0, H-10); 7.39 (2H, d, ^3J = 8.0, H-3',5'); 7.18 (1H, d, ^3J = 8.0, H-2); 3.07 (3H, s, CH_3)
5	3059, 3018, 1597 (C-O), 1491, 1377, 1346, 1328, 1088, 817, 757, 721	10.32 (1H, s, H-6); 8.57 (1H, d, ^3J = 6.5, H-4); 8.26 (1H, d, ^3J = 8.0, H-7); 7.80 (1H, t, ^3J = 8.0, H-9); 7.73 (1H, t, ^3J = 8.0, H-8); 7.65-7.50 (3H, m, H-3,2',6'); 7.40 (1H, d, ^3J = 8.0, H-10); 7.30 (2H, d, ^3J = 8.5, H-3',5'); 6.33 (1H, d, ^3J = 8.0, H-2)
6	3008, 2992, 2966, 1770 (C=O), 1382, 1362, 1315, 1184 (C-O), 1163, 788	10.97 (1H, s, H-6); 9.45 (1H, d, ^3J = 6.5, H-4); 8.26 (1H, m, H-7); 8.08-8.05 (3H, m, H-3,8,9); 7.88 (1H, d, ^3J = 8.0, H-10); 7.74 (2H, d, ^3J = 8.5, H-2',6'); 7.47-7.45 (3H, m, H-2,3',5'); 1.60 (3H, s, CH_3)



5 **4c** **6**

$R^1 = 4\text{-}ClC_6H_4$

1-Hydroxyacridizinium salts **4** displayed properties typical for phenols and gave a red-violet color in neutral aqueous $FeCl_3$ solutions. These compounds also may be acylated at the oxygen atom. Thus, 1-acetoxypyrido[1,2-*b*]isoquinolinium bromide **6** was obtained upon heating the salt **4c** in acetic anhydride, as indicated by the ^1H NMR signal for the H-4 proton at 9.45 ppm and acetyl group at 1.60 ppm, as well as the $\nu_{C=O}$ stretching band at 1770 cm^{-1} in the IR spectrum.

Thus, we have discovered a new means for adding an isoquinoline ring to a pyridine ring using an electrophilic aromatic substitution reaction, which yields 1-hydroxyacridizinium salts.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer Spectrum BX spectrometer for KBr pellets. The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 with TMS as internal standard. The melting points were determined in a Thiele apparatus. The purity of the products was checked by HPLC on an Agilent 1100 Series c instrument with an Agilent LC/MSDSL selective detector using atmospheric pressure chemical ionization (400 V). Gradient elution was carried out with phase A) H_2O + 0.1% HCO_2H, phase B) MeCN + 0.1% HCO_2H. The elemental analysis was carried out using a Vario MICRO cube CHNS analyzer. The Schoeniger method was used to determine halogens. 2-(Bromomethyl)benzaldehyde (**1a**) was prepared according to Zhang and Lippard [15], while [2-(bromomethyl)phenyl](4-chlorophenyl)methanone (**1b**) was obtained according to Kim et al. [16] and [2-(bromomethyl)-5-nitrophenyl](phenyl)methanone (**1c**) was obtained as a mixture containing 70% methanone **1c** according to Gobbi et al. [17]. A sample of methyl 2-(bromomethyl)benzoate (**1d**) was prepared according to Osdene and Timmis [18]. Pyridines **2a-h** were obtained from Sigma-Aldrich.

1-Benzylpyridinium bromides 3a-e,h-l (General Method). Pyridine **2a-e**,**h-l** (5.5 mmol) was added to a solution of benzyl bromide **1a-e**,**h-l** (5.0 mmol) in anhydrous acetone (10 ml), and the mixture obtained was maintained for 72 h at room temperature. The precipitate formed was filtered off and washed with acetone. All products **3** here and hereinafter were washed with acetone.

1-(2-Formylbenzyl)pyridinium Bromide (3f). Pyridine **2d** (0.44 g, 5.5 mmol) was added to a solution of aldehyde **1a** (1.00 g, 5.0 mmol) in anhydrous benzene (10 ml). The mixture was maintained for 24 h at room temperature. The precipitate of bromide **3f** was filtered off.

1-[2-(4-Chlorobenzoyl)benzyl]pyridinium Bromide (3g). A mixture of ketone **1b** (0.5 g, 1.6 mmol) and pyridine (**2d**) (0.15 ml, 1.8 mmol) in anhydrous acetone (10 ml) was maintained for 2 h at 40-50°C and then heated at reflux for 1 h. After cooling, the precipitate of bromide **3g** was filtered off.

3-Hydroxy-1-[2-(methoxycarbonyl)benzyl]pyridinium Bromide (3m). Product **3m** was obtained according to the method for the preparation of compound **3f** from ester **1d** and pyridine **2a**, maintaining the reaction mixture at 60-70°C.

3-Hydroxy-1-(2-benzyloxycarbonyl)pyridinium Bromide (3n). Product **3n** was obtained according to the procedure for the preparation of products **4a-d** from salt **3m**, maintaining the reaction mixture for 10 h.

1-Hydroxypyrido[1,2-*b*]isoquinolinium Bromides 4a-d (General Method). A solution of salt **3a-e** (2.5 mmol) in 48% aqueous hydrobromic acid (20 ml) was heated at reflux for 2-3 h (salts **3b**,**e**), 6 h (salt **3a**), and 30 h (salts **3c**,**d**). After cooling, the precipitate formed of the corresponding bromide **4** was filtered off and washed with acetone.

11-(4-Chlorophenyl)pyrido[1,2-*b*]isoquinolinium-1-olate (5). A solution of salt **4c** (0.39 g, 1 mmol) in a mixture of Et_3N (0.5 ml, 3.6 mmol) and methanol (20 ml) was stirred at room temperature for 30 min. The solvent was evaporated in vacuum. Then, 2-propanol (15 ml) was added to the residue. The mixture was heated to reflux. After cooling, the precipitate of product **5** was filtered off and washed with 2-propanol.

1-(Acetoxy)-11-(4-chlorophenyl)pyrido[1,2-*b*]isoquinolinium bromide (6). A mixture of salt **4c** (0.3 g, 0.8 mmol) and acetic anhydride (10 ml) was heated at reflux for 20 min. After cooling, diethyl ether (50 ml) was added. The precipitate of bromide **6** was filtered off and washed with 2-propanol.

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