THE SYNTHESIS OF CONDENSED QUINOLIZINIUM SYSTEMS‡

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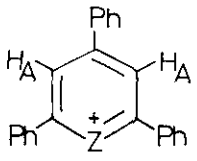
Abstract - Dimethyl β-aminoethylacetal reacts with pyryliums (1-3a) to yield pyridiniums (1-3b) which are cyclised to fused benzoquinolizinium (4-6).

Bradsher and Beavers[1] prepared the first fully aromatic benzoquinolizinium derivatives by cyclodehydration of 1-acetonyl- and 1-phenacyl-2-phenylpyridiniums. Reactions of this general type have been reviewed.[2,3] Chloroacetaldoxime was previously used as a quaternising agent to give the equivalent of 1-β-oxyethyl substituent.[4] We now find that dimethyl β-aminoethylacetal can be used as an alternative route to such compounds. This acetal reacts with pyryliums to yield 1-β,β-dimethoxyethyl derivatives which have led to syntheses of the condensed ring systems 4, 5 and 6. Ring systems 5 and 6 were previously unreported.

Dimethyl β-aminoethylacetal condensed with pyryliums 1a, 2a and 3a to give the expected pyridiniums 1b, 2b and 3b (Table 1) by the usual method.[5] On treatment with strong acid, each of the N-(β,β-dimethoxyethyl)pyridiniums cyclised to form quinolizinium salts (4-6) (Table 2), presumably via the carbonium ion intermediates (1c-3c).



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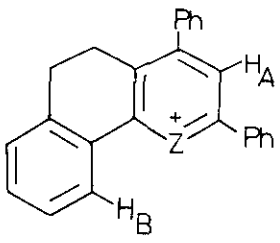

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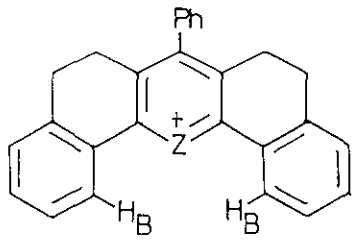

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a Z = O
b Z = $NCH_2CH(OMe)_2$
c Z = $N^+CHCHOMe$

‡Submitted in honour of the retirement of Dr. Tetsuji Kametani, Founder and Chief Editor of "Heterocycles" with profound good wishes.

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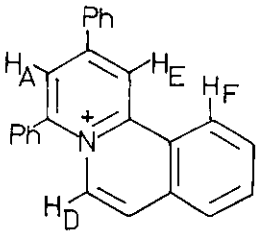
Table 1: Preparation of pyridiniums (1b-3b), and quinoliziniums (4-6)

Compound no.	Yield %	Mp (°C)	Crystal form[a]	Found % C	H	N	Formula	Required % C	H	N
1b	54	178-179	plates	67.0	5.3	2.9	$C_{27}H_{26}BF_4NO_2$	67.1	5.4	2.9
2b	57	154-155	plates	62.6	4.8	2.4	$C_{30}H_{28}F_3NO_5S$	63.0	4.9	2.4
3b	78	256-257	plates	69.4	5.5	2.5	$C_{31}H_{30}BF_4NO_2$	69.6	5.6	2.6
4[b]	76	231-232	needles[c]	68.2	4.3	3.2	$C_{25}H_{20}BF_4NO$	68.6	4.6	3.2
5	86	196-197	prisms	66.1	3.9	2.7	$C_{28}H_{20}F_3NO_3S$	66.3	3.9	2.8
6	64	254-256	needles	74.2	4.5	3.0	$C_{29}H_{22}BF_4N$	73.9	4.7	3.0

a) From MeOH unless otherwise indicated. b) Monohydrate. c) From 80% aqueous EtOH.



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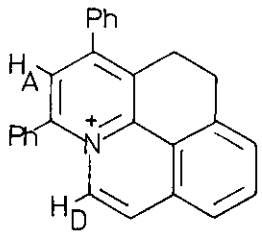

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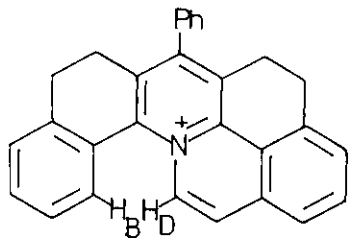

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The structures of the cyclised products 4-6 are supported by the ^{1}H nmr data (Table 2). In the case of 1b and 3b the direction of cyclisation is unambiguous, and the spectra are satisfactorily interpreted on the basis of structures 4 and 6. However, 2b could cyclise to yield either 5 or 7; a distinction between these two structures is achieved by comparison of the spectra with those of the products 4 and 6.

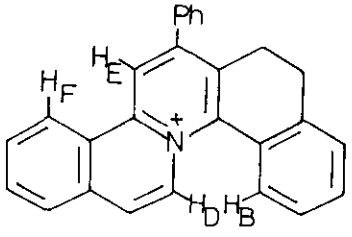
The ^{1}H nmr of 7 would be expected to have at least four deshielded (δ 8.5-9.5) resonances as found in 4: most downfield being H_D doublet and H_E singlet (ca δ 9), with H_F and H_B (ca δ 8.5) multiplets (1,2 and 1,3 coupling) next most downfield due to steric polarisation; and H_A should be absent. Similar downfield shifts are observed in photocyclised heterocycle 8.[6] In fact we find only one deshielded proton at 8.4 for H_D. In other respects, the product from 2b has a spectrum similar to that of 6 (cf CH_2CH_2 at δ 3.2 and 2.9 in 6 and at δ 3.4 in 5) and therefore it is assigned structure 5. Further evidence for structure 5 comes from uv: $\lambda_{max.}$ for 4 and 6 are respectively 376 and 400 nm. The product from 2b has $\lambda_{max.}$ = 376 nm, consistent with structure 5; 7 should have $\lambda_{max.}$ similar to that of 6.

Nucleophilic attack on the benzo[a]quinolizinium ring (cf 9) has previously[7] occurred at the 4-position, with ring-opening to an isoquinoline. When piperidine is reacted with 4, pyridine 10 is obtained. Presumably the phenyl at position-4 in quinolizinium 4 hinders approach of piperidine: hence ring opening preferentially to pyridine 10 occurs.

Table 2: ^{1}H Nmr data[a]

Cpd. no.	Aromatic A (s) δ	B (m) δ	D (1H, d) δ	J	E (1H, m) δ	J	F (1H, m) δ	Residual aromatics (m) δ	Aliphatic N^{+}-CH_2 (2H, d) δ	J	$CH(OMe)_2$ (1H, t) δ	J	OCH_3 (6H, s) δ	C_2H_4 (m) δ
1b	7.9 (2H)	-	-		-		-	7.5-8.0 (15H)	4.7	6	3.9	6	2.9	-
2b	7.8 (1H)	8.2 (1H)	-		-		-	7.3-7.6 (13H)	5.2	4	3.9	4	2.9	2.7 (4H)
3b	-	8.1 (2H)	-		-		-	7.4-7.7 (11H)	5.5[b]	4	4.0[b]	4	2.9	2.9 (8H)
4[c]	8.2 (1H)[d]	-	8.5	8	9.4	3	9.0	7.5-8.1 (14H)	-		-		-	-
5	8.0 (1H)	-	8.4	8	-		-	7.5-7.8 (14H)	-		-		-	3.4 (4H)
6[e]	-	8.0 (1H)	9.2	7	-		-	7.4-7.7 (12H)	-		-		-	3.2 (4H) 2.9 (4H)

[a] In $CDCl_3$ unless otherwise indicated. [b] Broadened. [c] In CF_3CO_2H. [d] d, J 3 Hz.
[e] In $(CD_3)_2SO$.



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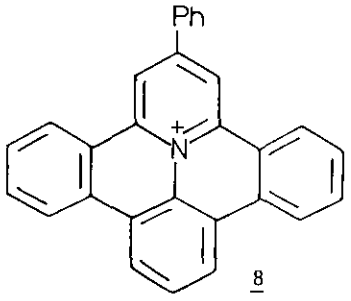

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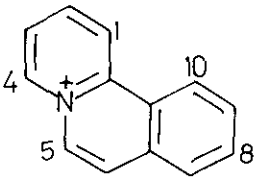

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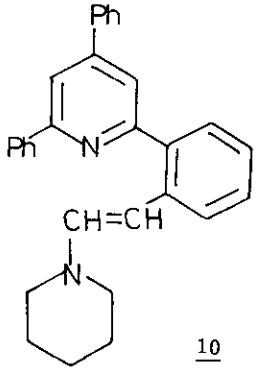

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EXPERIMENTAL

Ir and ^{1}H nmr spectra were recorded on Perkin-Elmer 257 and Perkin-Elmer R12 instruments respectively. *Mps are uncorrected* and were obtained on a Kofler hot stage apparatus.

Preparation of Acetals (1b, 2b and 3b). *The pyrylium* salt (10 mmol) was suspended in CH_2Cl_2 (5 ml); β,β-dimethoxyethylamine (10 mmol) and triethylamine (5 mmol) were added and the mixture was stirred for 40 min. *Acetic acid (0.1 ml) was* added and the mixture stirred for a further 12 min. After pouring into ether (200 ml), the resulting crystals were removed by filtration and washed with water, then with ether.

Preparation of Quinoliziniums (4, 5 and 6). Acetal (1b, 2b or 3b, 5 mmol) was heated at 100°C in water (25 ml) and the appropriate acid (fluoroboric for 1b and 3b; *trifluoro*-methanesulphonic for 2b, 25 ml) for 1.5 h. The mixture was allowed to cool to ca 25°C and then the product was extracted into CH_2Cl_2 (50 ml), poured into ether (200 ml), and stirred. Crystals were isolated by filtration, washed with water, and then with ether (Table 1).

2-(2-Piperidinioethenyl)-4,6-diphenylpyridine (10). Compound 4 (1 g, 2.4 mmol) was maintained at ca 108°C in piperidine (20 ml) for 5 days. Water (50 ml) was added and the product was extracted into ether (10 x 15 ml). The ethereal layer was washed with water (3 x 20 ml), dried over $MgSO_4$, and removal of the solvent at ca 20°C/25 mmHg gave the pyridine 10 (0.72 g, 76%), prisms from n-hexane, m.p. 143-145°C (Found: C, 86.2; H, 6.7; N, 6.4. $C_{30}H_{28}N_2$ requires C, 86.5; H, 6.8; N, 6.7%); δ (CCl_4) 8.2 (2 H, m), 7.0-7.8 (14 H, m), 6.4 (1 H, d, J 13 Hz), 5.6 (1 H, d, J 13 Hz), 2.8 (4 H, m), 1.4 (6 H, m).

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