1-ETHOXYCARBONYLQUINOLIZINIUM SALTS CONDENSATION OF β-KETOENOL ETHERS WITH 2-PYRIDYLACETATES

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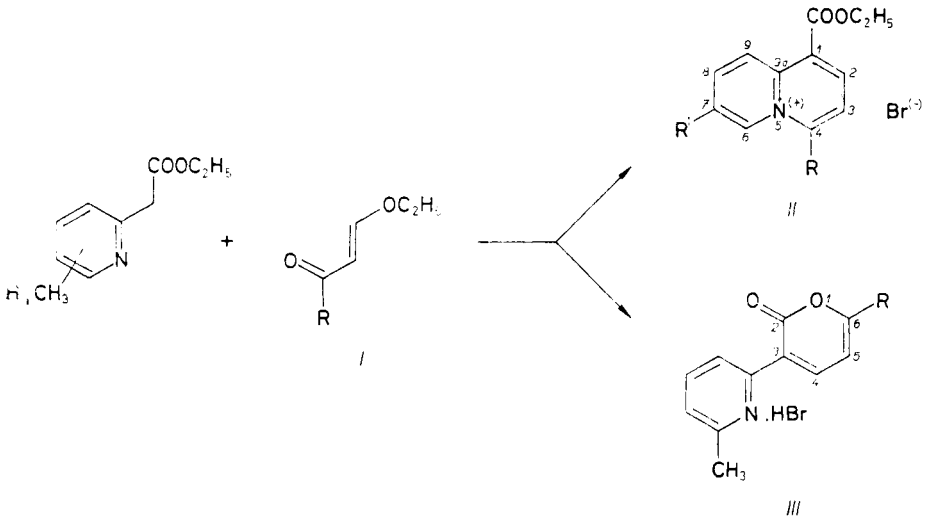
A general route to some 1-ethoxycarbonylquinolizinium bromides has been worked out. The method allows to conduct the condensation between β-ketoenol ethers and substituted 2-pyridylacetates in homogenous conditions in the presence of trifluoroacetic acid in an aprotic solvent. The substitution at C-6 in 2-pyridylacetates completely changes the reaction course affording 3,6-disubstituted 2-pyrones.

In the total synthesis of some Nuphar alkaloids it was found the quinolizinium derivatives to be convenient intermediates[1]. We wish to report now the general procedure for preparation of 1-ethoxycarbonylquinolizinium bromides together with the scope and limitations of the method.

The title compounds were prepared by the condensation of 2-pyridylacetates with ketoenol ethers *I* (Scheme 1). Simple derivatives of β-diketo compounds like diethylacetals[2] enol ethers[3] and β-diketones themselves[4] have been already used in preparation of quinolizinium salts[5].

Our method allows to conduct the condensation in homogeneous conditions because of solubility of trifluoroacetates in aprotic solvents. Progress of the reaction has been controlled measuring amounts of water separated in a Dean–Stark apparatus. The second step allows to finish the condensation and easy separation of the bromide. We found the reaction yield depends on the type of enol ether used and slightly on the reaction scale (when varied from 0·02 to 0·2 mol). On the other hand the substitution pattern of 2-pyridylacetate appeared to be a limiting factor. Condensations of enol ethers having an alkyl (R = Me), aryl (R = Ph) or heterocyclic substituent (R = 2- or 3-furyl and 2-thienyl) with unsubstituted or 5-substituted 2-pyridyl acetates yield corresponding quinolizinium salt *II*. 6-Methyl substituted quinolizinium salts could not be obtained by the method and in these cases hydrobromides of α-pyrones *III* were the only crystallizable products. We believe that the change in the reaction course is due to the steric factor of 6-methyl substituent.

^{1}H NMR data of the products are given in Table I (for *II*) and Table II (for *III*) and ^{13}C NMR data of quinolizinium bromides in Table III.



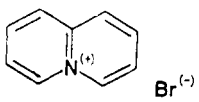
	R
Ia	CH_3
Ib	C_6H_5
Ic	2-furyl
Id	3-furyl
Ie	2-thienyl

	R	R'
IIa	CH_3	H
IIb	C_6H_5	H
IIc	2-furyl	H
IId	3-furyl	H
IIe	2-thienyl	H
IIf	C_6H_5	CH_3
IIg	2-furyl	CH_3
IIh	3-furyl	CH_3

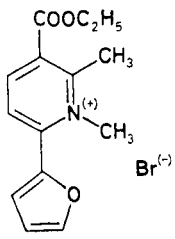
	R
IIIa	CH_3
IIIb	C_6H_5
IIIc	2-furyl
IIId	3-furyl
IIIe	2-thienyl

SCHEME 1

Assignments of ^{13}C quinolizinium resonances were made on the basis of chemical shift correlation with data of the parent quinolizinium bromide *IV* and 3-ethoxycarbonyl-6-(2-furyl)-1,2-dimethylpyridinium bromide (*V*) using general rules for substituent influences on carbon chemical shifts in heteroaromatic systems[7].



IV



V

Enol ethers *I* with R = Me, Ph, 2- or 3-furyl, and 2-thienyl moieties were easily prepared from corresponding methyl ketones and ethyl formate using sodium hydride or sodium[7] as the condensing agents followed by alkylation with diethyl sulfate or ethyl bromide in N,N-dimethylformamide at 60°C.

As it is clearly seen from ^{1}H NMR data (Table IV) we obtained pure *E*-isomers of all β-ketoenol ethers ($^4J^E$(H, H) = 12 Hz vs 7·5 Hz in *Z*-isomer) while the slightly different method of Spassky[8] furnished a 3 : 1 mixture of *Z*- and *E*-isomers of 3-ethoxyacrylophenone (*Ib*). Yields of conversion of sodium enolates into ethyl enol ethers were the same when either diethyl sulfate or ethyl bromide were used. ^{1}H NMR spectra of the products obtained by ethyl bromide alkylation showed that traces of C-alkylation impurities were present.

TABLE I

^{1}H NMR assignments of 1-ethoxycarbonylquinolizinium bromides *II* (in CD_3SOCD_3 with TMS; chemical shifts in ppm)

Compound	H-2[a]	H-3	H-6	H-8	H-9	R^1	R^b
IIa	8·84 d	8·21 d	9·46 br d	8·62 br t	9·30 br d	8·27 br t (H-7)	3·15 s (CH_3)
IIb	9·00 d	8·16 d	9·31 br d	8·64 br t	9·06 br d	8·15 br t (H-7)	7·44 s (C_6H_5)
IIc	8·91 d	8·46 d	9·72 br d	8·69 br t	9·33 br d	8·29 br t (H-7)	7·69 d (H-3′); 6·95 dd (H-4′); 8·32 d (H-5′)
IId	8·88 d	8·25 d	9·39 br d	8·66 br t	9·30 br d	8·23 br t (H-7)	8·52 m (H-2′); 7·08 m (H-4′); 8·03 m (H-5′)
IIe	8·86 d	8·22 d	9·46 br d	8·64 br t	9·29 br d	8·16 br t (H-7)	7·79 dd (H-3′); 7·43 dd (H-4′); 8·16 dd (H-5′)
IIf	8·84 d	8·09 d	8·80 br s	8·52 br d	9·22 d	2·52 s (CH_3)	7·76 br s (C_6H_5)
IIg	8·80 d	8·38 d	9·43 br s	8·50 br d	9·23 d	2·68 s (CH_3)	7·73 d (H-3′); 7·00 dd (H-4′); 8·30 d (H-5′)
IIh	8·77 d	8·17 d	9·13 br s	8·42 br d	9·20 d	2·62 s (CH_3)	8·43 m (H-2′); 7·10 m (H-4′); 8·12 m (H-5′)

[a] Coupling constants of quinolizinium nucleus protons were: $J(2, 3) = J(6, 7) = J(7, 8) = 8$, $J(8, 9) = 9$ Hz; [b] Coupling constants of other heterocyclic substituent protons were: 2-furyl ($J(3', 4') = 4$, $J(4', 5') = 2$ Hz); 2-thienyl ($J(3', 4') = 3·5$, $J(3', 5') = 1$, $J(4', 5') = 5$ Hz).

This method of quinolizinium salt synthesis has recently been adapted to the preparation of C-7 oxygenated derivatives[9].

EXPERIMENTAL

Melting points and boiling points are uncorrected. Spectra of *II* and *III* were determined as follows: ^{1}H NMR in CD_3SOCD_3 with TMS at 100 MHz on a Jeol JNM-4H-100 or at 80 MHz on a Tesla BS-487B spectrometers. ^{13}C NMR fully proton noise and off-resonance spectra on a Jeol FX 90 Q instrujent operating at 22·5 MHz at temperature 35°C in (FT mode) D_2O (0·5 mol l^{-1} concentrations or saturated solutions) with internal dioxane (δ 67·3 ppm). Chemical shifts are given in ppm (δ-scale).

(*E*)-1-Ethoxy-2-furoylethylene (*Ic*)

Sodium enolate of 2-furoylacetaldehyde[10] (68·0 g, 0·425 mol) was dissolved upon heating in DMF (430 ml), the solution was cooled to room temperature and diethyl sulfate (65·6 g, 0·425 mol) was dropped into the stirred solution. After 1 h of stirring at 50—60°C the solution was concentrated in vacuum to c. 100 ml. The residue was taken up with benzene (500 ml) and washed with water. The water layer was washed twice with benzene and the combined organic extracts were dried over anhydrous magnesium sulfate. After removal of the solvent a residual brown oil was distilled in vacuum yielding 27 g of a light yellow solid. For other data see Table IV.

The compounds *Ia*, *Ib*, *Id*, and *Ie* were prepared in the same manner.

TABLE II

^{1}H NMR assignments for α-pyrones *III* (in CD_3SOCD_3 with TMS; chemical shifts in ppm)

Compound	Pyrone nucleus		Pyridine nucleus			CH_3[b]	R[c]
	H-4[a]	H-5	H-3	H-4	H-5		
IIIa	6·44 d	8·50 d	8·07 d	7·72 t	7·21 d	2·50 s	2·32 s (CH_3)
IIIb	7·30 d	8·55 d	8·15 d	7·77 t	7·22 d	2·50 s	7·8 m (C_6H_5)
IIIc	6·90 d	8·47 d	8·11 d	7·71 t	7·20 d	2·50 s	7·19 d (H-3′); 6·75 dd (H-4′); 8·04 d (H-5′)
IIId	7·09 d	8·49 d	8·14 d	7·72 t	7·20 d	2·50 s	7·83 dd (H-3′); 7·25 dd (H-4′); 7·88 dd (H-5′)

[a] Coupling constants were as follows: pyrone nucleus $J(4, 5) = 7$; pyridine nucleus $J(3, 4) = J(4, 5) = 8$ Hz; [b] hidden by DMSO trace signal (revealed when the spectrum was taken in $CDCl_3$); [c] coupling constants in 2-furyl and 2-thienyl systems same as in Table I.

TABLE III

^{13}C NMR assignments for 1-ethoxycarbonylquinolizinium bromides *II* (in D_2O with dioxane, chemical shifts in ppm)

Compound	Carbon atom															
	1	2	3	4	6	7	8	9	9a	1′ or 5′	2′	3′	4′	C=O	CH_2	CH_3CH_2	CH_3
IIa	126·6	139·8	125·1[a]	149·0	134·0	124·9[a]	138·5	126·4	142·8	—	—	—	—	165·4	64·7	14·3	21·8
IIb	127·6	139·9	125·1[a]	150·3	135·7	125·8[a]	139·4	126·5[a]	143·3	131·8	130·7	130·1	132·5	165·5	64·9	14·3	—
IIc	127·0	139·7	124·8	139·7	135·6	126·5	139·7	125·5	143·0[a]	148·7	143·7[a]	119·7	114·0	165·0	64·9	14·3	—
IId	127·5	139·8[a]	125·2	143·5[b]	135·6	126·5	139·4[a]	125·8	143·4[b]	146·0	146·5	117·9	110·9	165·4	64·8	14·1	—
IIe	127·9	139·6[a]	125·3	144·0[b]	135·8	127·1	139·4[a]	126·5	143·4[b]	129·6	131·0	133·6	133·1	165·4	64·9	14·2	—
IIf	127·5	138·8	125·6	149·5	133·5	136·8	141·5	125·6	141·5	132·1	130·7	130·0	132·4	165·6	64·8	14·1	18·8
IIg	126·8	141·9	124·8	143·8	133·4	137·5	138·6	125·7	141·2	148·6	139·0	119·6	113·9	165·0	64·9	14·2	19·1
IIh	127·3	138·8	125·3[a]	142·8	133·4	137·5	141·6	125·9[a]	141·4	145·9	146·5	118·1	110·9	165·3	64·8	14·0	19·2
IV[c]	127·9	137·6	124·7	137·0[d]	137·0[d]	124·7	137·6	127·9	143·1[e]	—	—	—	—	—	—	—	—
	126·8	136·8	123·6	136·6[d]	136·6[d]	123·6	136·8	126·8	142·4[d]	—	—	—	—	—	—	—	—

[a,b] Values may be interchanged; [c] data for unsubstituted quinolizinium bromide, prepared by a method of Miyadera and Iwai[6], the values in the last row are taken from the spectrum run in CD_3SOCD_3 solution; [d] broadened; [e] very broad signal.

TABLE IV

Preparation and ^{1}H NMR data (at 80 MHz in $CDCl_3$ with TMS) of β-ketoenol ethers *I*

Compound[a]	Yield[b] %	B.p. (m.p.)	δ in ppm, *J* in Hz						
			H-3(2)	H-4	H-5	=C—C=O	=CH—O	CH_2	CH_3
Ia	24	75–80°C/1·33 kPa[c]							
Ib	52	148–150°C/0·80 kPa[d]							
Ic	38	103–106°C/67 Pa (50–52°C)[f]	7·15 d *J* = 4	6·52 dd *J* = 4 *J'* = 2	7·55 d *J* = 2	6·25[e] *J* = 12	7·80[e] *J* = 12	4·05 q *J* = 7	1·37 t *J* = 7
Id	54	104–107°C/27 Pa (74–76°C)[f]	7·98 m	6·78 m	7·42 m	6·00[e] *J* = 12	7·70[e] *J* = 12	4·02 q *J* = 7	1·37 t *J* = 7
Ie	46	128–134°C/67 Pa (47–49°C)[g]	7·54 dd *J* = 4 *J'* = 1	7·00 dd *J* = 5 *J'* = 4	7·47 dd *J* = 5 *J'* = 1	6·19[e] *J* = 12	7·67[e] *J* = 12	4·03 q *J* = 7	1·35 t *J* = 7

[a] Elemental analyses are accurate within 0·40% C and 0·35% H; [b] starting from methylketones; [c] literature[11] gives b.p. 91–93°C/2·66 kPa; [d] literature[8] gives b.p. 151–155°C/2·66 kPa; [e] AB system; [f] from ether; [g] from hexane.

1-Ethoxycarbonyl-4-(2-furyl)quinolizinium Bromide (*IIc*)

Benzene (80 ml) solution of enol ether *Ic* (4·15 g, 30 mmol), ethyl 2-pyridylacetate (4·12 g, 25 mmol) and trifluoroacetic acid (3·8 ml, 50 mmol) was heated for 5 h with azeotropic removal of evolving water (0·5 ml). 45% hydrobromic acid in acetic acid (4·5 ml) was added and trifluoroacetic acid–benzene mixture (30 ml) was distilled off. The azeotropic removal of water was continued for another 3 h, the solvent was evaporated in vacuum and the residual oil was

TABLE V

Condensation of β-ketoenol ethers *I* with 2-pyridylacetates

Product	Yield %	M.p. °C	Formula (M.w.)	Calculated/Found		
				% C	% H	% N
IIa	52	158—160	$C_{13}H_{14}BrNO_2$ (296·2)	52·71 [a]	4·76 [a]	4·73 [a]
IIb	38	161—169	$C_{18}H_{16}BrNO_2$ (358·2)	60·36 [a]	4·50 [a]	3·91 [a]
IIc	52	157—163	$C_{16}H_{14}BrNO_3$ (348·2)	55·19 [a]	4·05 [a]	4·02 [a]
IId	61	167—170	$C_{16}H_{14}BrNO_3$ (348·2)	55·19 55·15	4·05 3·94	4·02 3·98
IIe	37	137—144	$C_{16}H_{14}BrNO_2S$ (364·2)	52·76 [a]	3·87 [a]	3·85 [a]
IIf	40	180—183	$C_{19}H_{18}BrNO_2$ (372·3)	61·30 61·00	4·87 5·09	3·76 3·78
IIg	42	178—180	$C_{17}H_{16}BrNO_3$ (362·2)	56·37 56·61	4·45 4·32	3·87 3·86
IIh	23	195 (dec.)	$C_{17}H_{16}BrNO_3$ (362·2)	56·37 56·61	4·45 4·61	3·87 3·86
IIIa	30	86—88	$C_{12}H_{11}NO_2$ (201·2)	71·63 [a]	5·51 [a]	6·96 [a]
IIIb	50	128—132	$C_{17}H_{13}NO_2$ (263·3)	77·55 77·53	4·98 4·98	5·32 5·48
IIIc	52	111—113	$C_{15}H_{11}NO_3$ (253·3)	71·14 70·73	4·38 4·34	5·53 5·34
IIIe	45	130—133	$C_{15}H_{11}NO_2S$ (269·3)	66·90 66·51	4·12 4·20	5·20 5·38

[a] Some bromides readily formed hydrates and were difficult to dehydrate even by prolonged drying at 100°C in vacuo.

taken up with acetone. After 3 days at 0°C a small amount of contaminant precipitate was filtered off and discarded. The filtrate was concentrated to about 10 ml and left for one week period at 0°C after addition of dry ether (20 ml). Resulting brown crystals (1·50 g) of *IIc* were separated and washed with acetone (m.p. 156–162°C). After prolonged standing at the same temperature a second crop of the crude product (1·33 g) separated. Total yield 32%. For other data see Table V.

The compounds *IIa*, *IIb*, and *IId–IIh* were prepared in the same manner.

6-(2-Furyl)-3-(6-methylpyridyl)-2-pyrone (*IIIc*)

Condensation of *Ic* (4·15 g, 30 mmol) with ethyl 6-methyl-2-pyridylacetate (4·47 g, 25 mmol) was carried out in the same manner as above. It gave hydrobromide of *IIIc* with 48% yield. Pyrone *IIIc* can be freed quantitatively treating its hydrobromide aqueous solution with sodium carbonate and subsequent extraction of the precipitated product with ether. For other data see Table V.

The compounds *IIIa*, *IIIb*, *IIId*, and *IIIe* were prepared in the same manner.

Quinolizinium Bromide (*IV*)

Quinolizinium bromide was prepared by a known method[6]. The ^{13}C NMR data given in Table III when using deuterium oxide as the solvent are slightly different comparing ones recently published[12].

3-Ethoxycarbonyl-6-(2-furyl)-1,2-dimethylpyridinium Bromide (*V*)

We found this model compound is not available by direct methylation of the respective base. It forms in Hantzsch condensation between sodium enolate of 2-furoylacetaldehyde and ethyl β-methylaminocrotonate in conditions given in ref.[10], m.p. 189–190°C. ^{13}C NMR spectrum (D_2O–dioxane): 166·1 (s, C=O), 158·6 (s, C2), 149·6 (d, C5′), 148·8 (s, C2′), 145·0 (d, C4), 144·6 (s, C6), 130·0 (s, C3), 125·5 (d, C5), 122·0 (d, C3′), 114·4 (d, C4′), 64·7 (t, OCH_2), 44·6 (q, NCH_3), 19·7 (q, CH_3 at C2), 14·1 (q, ester CH_3).

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