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Abstract

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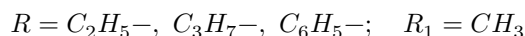
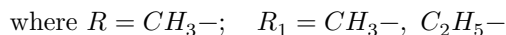
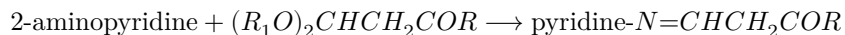
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SYNTHESIS OF SALTS OF 4-ALKYL-1-AZADEHYDROQUINOLIZINIUM

In a series of previous works published by us and by N. K. Kochetkov with co-workers, the synthesis of a number of nitrogen- and oxygen-containing heterocyclic systems was carried out (¹⁻¹⁰). In doing so, we proceeded from β -chlorovinyl ketones or the nearest products of their transformation. Recently, the attention of investigators has increasingly been attracted by the synthesis of fused aromatic heterocyclic systems in which the heteroatom is ammonium nitrogen common to two rings, in particular salts of dehydroquinolizinium (I). In contrast to quinoline and isoquinoline, the chemistry of the dehydroquinolizinium ion (¹¹⁻¹³) has been little studied. In the present work we have carried out the synthesis of a number of derivatives of a new fused heterocyclic system, the aza analog of dehydroquinolizinium (II). Salts of 4-alkyl-1-azadehydroquinolizinium were obtained by us from α -aminopyridine and β -ketoacetals. The latter are obtained in good yields from β -chlorovinyl ketones by the method developed by us jointly with N. K. Kochetkov (¹⁴).

(I) (II)

We found that β -ketoacetals enter into a condensation reaction with α -aminopyridine. It was established that the acetal group enters into the reaction, since on condensation with α -aminopyridine both the dimethyl acetal and the diethyl acetal of acetoacetaldehyde gave one and the same reaction product, namely 2-acetoacetalamino-pyridine:



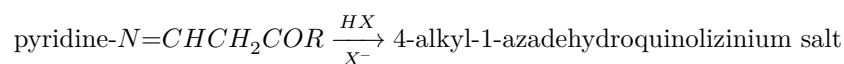
The 2-acylacetalamino-pyridines obtained are colorless or slightly colored substances, which crystallize with difficulty from various organic solvents.

Under the action of concentrated acids, the condensation products of α -aminopyridine with β -ketoacetals of the fatty series cyclize with elimination of water, forming a new heterocyclic system—salts of 4-alkyl-1-

Fig. 1

Figure 1: Fig. 1

azadehydroquinolizinium. The best results were obtained when hydrochloric and hydrobromic acids were used:



where $R = CH_3-$, C_2H_5- ; $X = Br$, ClO_4 .

$R = C_3H_7-$; $X = ClO_4$

However, such cyclization does not occur in the case $R = C_6H_5$. On attempting to carry out this reaction with aqueous acid, salts of α -aminopyridine and acetophenone were obtained, while under the action of gaseous hydrogen bromide in ether, α -aminopyridine hydrobromide and tribenzoylbenzene are formed.

The salts of 4-alkyl-1-azadehydroquinolizinium obtained are crystalline substances, readily soluble in water, moderately in

* The spectroscopic part of the work was carried out by N. K. Bel'skii.

in hot alcohol, insoluble in ether and benzene. Their perchlorates are more stable than the bromides. The structure of these salts is confirmed by the following facts. Aqueous solutions of these salts do not decolorize a weak solution of potassium permanganate and, consequently, do not contain nonaromatic double bonds. Under the action of alkali, 4-methyl-1-azadehydroquinolizinium bromide undergoes cleavage with formation of the starting 2-acetoacetylaminopyridine.

Fig. 1

Apparently, at first replacement of the anion by the hydroxyl group occurs, and then ring opening. Thus, upon cyclization of 2-acylacetylaminopyridines in an acidic medium no rearrangement takes place and, consequently, the alkyl substituent occupies position 4.

Upon catalytic hydrogenation over platinum, 4-methyl-1-aza-dehydroquinolizinium bromide absorbs five moles of hydrogen, which indicates the presence of five double bonds in two fused rings. Hydrogenation gives 4-methyl-1-aza-octahydroquinolizine hydrobromide.

The absorption spectra of aqueous solutions of the salts in the ultraviolet region were recorded (Fig. 1). The absorption curve of the 1-aza-dehydroquinolizinium ion is very characteristic and has six maxima (λ_{\max}), coinciding for all the

salts examined: 336, 318, 312, 304, 274, 228 $m\mu$ (Fig. 1). From the spectral data it is evident that the character of the spectrum is determined by the aza-dehydroquinolizinium nucleus.

The absorption region and the character of the spectrum of this nucleus are very similar to the region and character of the absorption of quinoline and isoquinoline, which also serves as confirmation of the structure we have adopted. The second nitrogen atom does, however, introduce some difference. The absorption spectrum of the aza-dehydroquinolizinium nucleus, like the absorption spectra of quinoline⁽¹⁵⁾ and isoquinoline⁽¹⁶⁾, is divided into three parts: 1) in the 350–290 $m\mu$ region there are several narrow and sharp absorption bands; 2) a broad band corresponds to the wavelength $\lambda = 282 m\mu$; 3) a broad intense band corresponds to the wavelength 228 $m\mu$. The distribution of intensities among the bands is also similar. For all these compounds, the intensities of the group of bands at 350–290 $m\mu$ and at 282 $m\mu$ differ little from one another; the short-wave band at 228 $m\mu$ is much more intense than all the others.

Experimental Part

2-Acylacetylaminopyridines. 2-Acylacetylaminopyridines were obtained by heating a mixture of 0.11 mole of α -aminopyridine and 0.1 mole of the corresponding β -ketoacetal in sealed ampoules for 5–6 hours to 140°. After the ampoule was opened, the crystallized reaction mass was pressed on a porous filter and washed repeatedly

ether. 2-Acylacetalamidopyridines were recrystallized from acetone or from a mixture of alcohol with petroleum ether (Table 2).

4-Methyl-1-azadehydroquinolizinium bromide. 1 g of 2-acetoacetalamidopyridine was dissolved in 1.2 ml of concentrated hydrobromic acid. To the solution were added 1.5 ml of alcohol and then ether—until a solid precipitate no longer separated. The precipitate was rapidly filtered off, washed with a mixture of absolute alcohol and ether (1 : 10), and then with absolute ether. Yield 1.1 g (75.8% of theory). Decomp. temp. 204–205° (begins to darken at 170°) after recrystallization from alcohol.

Found, %: C 47.82; 47.94; H 4.06; 4.11; N 12.29; Br 35.65
 $C_9H_9N_2Br$. Calculated, %: C 48.01; H 4.02; N 12.44; Br 35.55

Table 1

No.	Salt of 4-alkyl-1-azadehydroquinolizinium	Intensities $\epsilon \cdot 10^{-4}$
I	4-methyl-1-azadehydroquinolizinium bromide (structural formula shown; counterion Br^-)	0.7; 0.95; 0.75; 0.68; 0.5; 2.1

No.	Salt of 4-alkyl-1-azadehydroquinolizinium	Intensities $\epsilon \cdot 10^{-4}$
II	4-methyl-1-azadehydroquinolizinium perchlorate (structural formula shown; counterion ClO_4^-)	0.6; 1.0; 0.7; 0.69; 0.5; 0.48; 2.1
III	4-ethyl-1-azadehydroquinolizinium perchlorate (structural formula shown; counterion ClO_4^-)	0.8; 1.1 ; 0.8; 0.770.55; 2.1
IV	4- <i>n</i> -propyl-1-azadehydroquinolizinium perchlorate (structural formula shown; counterion ClO_4^-)	1.3 ; 1.2; 0.9; 0.8; 0.6; 1.8

4-Methyl-1-azadehydroquinolizinium perchlorate. A mixture of 1.2 g of 2-acetoacetalamidopyridine and 2 ml of 70% perchloric acid was heated on a water bath until the precipitate had completely dissolved, and then 3 ml of absolute alcohol was added. The colorless crystals that separated were filtered off and washed on the filter with absolute alcohol. Yield 1.4 g (77.3% of theory). Colorless scaly crystals. Decomp. temp. 226° (begins to darken at ~200°) after recrystallization from 50% methanol.

Found, %: C 44.14; 44.17; H 3.58; 3.63; N 11.52; 11.63; Cl 14.58; 14.32
 $\text{C}_9\text{H}_9\text{O}_4\text{N}_2\text{Cl}$. Calculated, %: C 44.26; H 3.71; N 11.46; Cl 14.48

4-Ethyl-1-azadehydroquinolizinium bromide. To 1.3 g of 2-propioacetalamidopyridine were added 2 ml of concentrated hydrobromic acid, then 1 ml of alcohol and 25-30 ml of ether. Yield 1.1 g (64.6% of theory). After recrystallization from a mixture of alcohol with ether, cream-colored crystals, m.p. 210-212°.

Found, %: C 49.98; 50.16; H 4.60; 4.60
 $\text{C}_{10}\text{H}_{11}\text{N}_2\text{Br}$. Calculated, %: C 50.20; H 4.60

4-Ethyl-1-azadehydroquinolizinium perchlorate. To 1 g of 2-propioacetalamidopyridine were added 1 ml of 70% perchloric acid and then 1 ml of absolute alcohol and 10 ml of ether. 1.09 g (74% of theory) of 4-ethyl-1-azadehydroquinolizinium perchlorate was obtained. After recrystallization from methanol, colorless scaly crystals, m.p. 169-170°.

Found, %: C 46.60; 46.42; H 4.33; 4.25; N 10.81; 10.96; Cl 13.78; 13.65
 $\text{C}_{10}\text{H}_{11}\text{O}_4\text{N}_2\text{Cl}$. Calculated, %: C 46.42; H 4.26; N 10.83; Cl 13.73

4-*n*-Propyl-1-azadehydroquinolizinium perchlorate. To a solution of 1 g

of 2-*n*-butyroacetalamidopyridine in 1.5 ml of 70% perchloric acid were added 10 ml of absolute alcohol, and then absolute ether was added until complete precipitation of the precipitate. Yield 0.95 g (64.2% of theory), m.p. 145°.

Found, %: C 48.67; 48.41; H 4.79; 4.75; N 10.21; 10.04; Cl 12.71; 12.60
 $C_{11}H_{13}O_4N_2Cl$. Calculated, %: C 48.57; H 4.77; N 10.23; Cl 13.02

Action of alkali on 4-methyl-1-azadehydroquinolizinium perchlorate.

To an aqueous solution of 2.3 g of perchlorate

Table 2

β -Ketoacetal	2-Acylacetal-aminopyridine	M.p., °C	Yield, %	Analysis data: found, %	Analysis data: calculated, %
CH_3COCH_2	$CH(OCH_3)_2$ pyridyl- $N=CHCH_2COCH_3$	121	61.3	C 66.56; 66.43H 6.27; 6.23N 17.40; 17.55	C 66.66H 6.17N 17.28
CH_3COCH_2	$CH(OC_2H_5)_2$ pyridyl- $N=CHCH_2COCH_3$	121	49.4	—	—
$C_2H_5COCH_2$	$CH(OCH_3)_2$ pyridyl- $N=CHCH_2COC_2H_5$	96.5-97	55.1	C 67.83H 6.71N 15.89	C 68.18H 6.81N 15.86
γ - $C_3H_7COCH_2$	2- $CH(OCH_3)_2$ b.p. $N=CHCH_2COC_3H_7$	86-88	65.7	C 69.40; 69.22H 7.38; 7.40N 14.62; 14.78	C 69.47H 7.37N 14.73
$C_6H_5COCH_2$	$CH(OCH_3)_2$ b.p. pyridyl- $N=CHCH_2COC_6H_5$	127-129 134- 135°/10	53.6	C 75.03; 74.82H 5.43; 5.41N 12.45; 12.47	C 74.97H 5.34N 12.50

To the solution of 4-methyl-1-aza-dehydroquinolizinium bromide was added 0.4 g of NaOH in 7 ml of water; the whole was shaken several times with benzene. The benzene extracts were washed with water and dried over sodium sulfate. The benzene was evaporated in vacuo; the crystalline residue (yield 1.4 g) has

m.p. 119°. A mixed melting-point test with 2-acetoacetalaminopyridine gives no depression.

Hydrogenation of 4-methyl-1-aza-dehydroquinolizinium bromide. 1 g of 4-methyl-1-aza-dehydroquinolizinium bromide in 150 ml of alcohol was hydrogenated over platinum black (300 mg) at room temperature and atmospheric pressure. 5 moles of hydrogen are absorbed. The resulting hydrobromide salt of 4-methyl-1-aza-octahydroquinolizine is difficult to purify; it was therefore identified as the picrate, m.p. 112° (from alcohol).

Found, %: N 18.15; 18.13

$C_{15}H_{21}O_7N_5$. Calculated, %: N 18.19

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