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SYNTHESIS OF PYRIDINIUM SALTS BY THE REACTION OF α, β-UNSATURATED KETONES, PRIMARY AMINES, AND COMPOUNDS WITH LABILE HYDROGEN ATOMS

V. A. Kaminskii, G. Ya. Shevchuk, and
M. N. Tilichenko

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The reaction of α, β-unsaturated ketones or Mannich bases of ketones with primary aromatic amines and ketones (monoketones or dimedone) in the presence of polyhaloalkanes leads to pyridinium, 5,6,7,8-tetrahydroquinolinium, or sym-octahydroacridinium salts. The reaction of benxalcyclohexanone with primary aromatic amines and malonodinitrile makes it possible to obtain 2-amino-3-cyano-5,6,7,8-tetrahydroquinolinium salts.

Examples of the synthesis of nitrogen-unsubstituted pyridine derivatives by the reaction of α, β-unsaturated ketones with ketones and ammonia (in the form of ammonium acetate) are known [1, 2]. A similar reaction of α, β-unsaturated ketones, ammonium acetate, and malonodinitrile gives 2-amino-3-cyanopyridine derivatives [3, 4]; 2-hydroxy-3-cyanopyridine derivatives are formed when malonodinitrile is replaced by cyanoacetic ester [5]. The preparation of N-substituted pyridinium salts via analogous schemes with primary amines in place of ammonia has not been described.

It has been previously shown that the reaction of 1,5-diketones with primary amines in the presence of oxidizing agents, viz., polyhaloalkanes, leads to N-substituted pyridinium salts [6, 7]; the one-step synthesis of 4-aryl-1-R-pyridinium salts by the reaction of ketones, aromatic aldehydes, and primary amines in the presence of CCl has also been described [8, 9].

We have shown that the reaction of α, β-unsaturated ketones with primary amines and compounds with a labile hydrogen atom in the presence of an oxidizing agent, viz., carbon tetrachloride or hexachloroethane, makes it possible to obtain a number of pyridinium salts. The use of C_2Cl_6 is preparatively more convenient and gives better yields of the salts than the use of CCl_4. The corresponding N-substituted dihydropyridines (products of a reaction of the type in the Hantzsch synthesis), which are subsequently oxidized by polyhaloalkanes, are possible intermediates in the reaction.

Benzalacetophenone, benzalpinacolone, and benzalcyclohexanone were used as the α, β-unsaturated ketones. As demonstrated in the case of β-dimethylaminopropiophenone (IIIa) and 2-(α-phenylamino-benzyl)cyclohexanone (IIIb), Mannich bases can be the source of α, β-unsaturated ketones. Monoketones, dimedone, and malonodinitrile were used as compounds with a labile hydrogen atom; cyanoacetic ester does not participate in the formation of pyridinium salts. The use of aromatic primary amines gives satisfactory results. In the case of aliphatic amines (benzylamine, cyclohexylamine, and ethanolamine) pyridinium salts were obtained in insignificant amounts; nitrogen-unsubstituted pyridines with corresponding structures are formed during the reaction, most likely as a consequence of aromatization of the intermediate N-alkyl-dihydropyridines with splitting out of a hydrocarbon [10, 11]. The reaction of IIIb with cyclohexanone or malonodinitrile without the addition of an amine was also carried out; the aniline formed in the deamination of amino ketone IIIb participated in the reaction.

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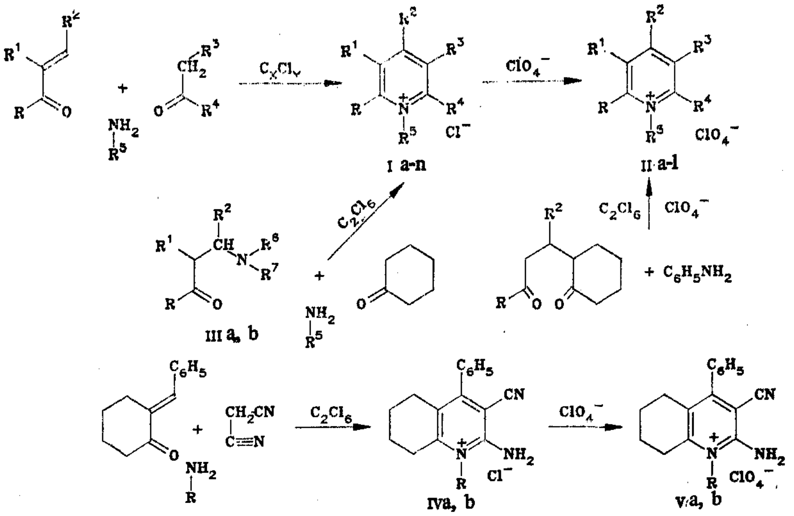

I, II a–e, g–i, k, m, n $R=C_6H_5$, f $R=tert\text{-}C_4H_9$, j, l $R+R^1=(CH_2)_4$; a–i, k, m, n $R^1=H$; a, b, f–m $R^2=C_6H_5$, c, n $R^2=C_6H_4OH\text{-}p$, d, e $R^2=H$, h $R^3=H$, h $R^3=C_6H_5$; a–f, j, m, n $R^3+R^4=(CH_2)_4$, q $R^3+R^4=(CH_2)_3$, k, l $R^3+R^4=COCH_2C(CH_3)_2CH_2$; h $R^4=C_6H_4NO_2\text{-}p$, i $R^4=C_2H_5$; a, c, d, f–l $R^5=C_6H_5$, b, e R^5=β-naphthyl, m, n $R^5=C_6H_4COOH\text{-}p$; III–Va $R=C_6H_5$; IIIa $R^1=R^2=H$, $R^6=R^7=CH_3$, b $R+R^1=(CH_2)_4$, $R^2+R^6=C_2H_5$, $R^7=H$; IV, Vb $R=C_6H_4OCH_3\text{-}p$

Pyridinium, 5,6,7,8-tetrahydroquinolinium, and sym-octahydroacridinium salts were obtained as a result of the indicated reactions. The initial reaction products are pyridinium chlorides Ia-n and IVa, b, which in most cases were converted to the readily isolable corresponding perchlorates IIa-l and Va, b; only chlorides Im, n were isolated in the form of crystal solvates with ethanol and IVa. 9-Phenyl-10-R-sym-octahydroacridinium perchlorates IIj (R = C_6H_5) and VI (R = $C_6H_4OCH_3$-p) were isolated as side products in the reaction of benxalcyclohexanone with amines and malonodinitrile and in the reaction of IIIb with malonodinitrile. Only salt IIj was obtained in the reaction of benzalcyclohexanone with aniline and cyanoacetic ester; 1, 2, 4, 6-tetraphenylpyridinium perchlorate (VII) was isolated from the reaction of benxalacetophenone with aniline and malonodinitrile. The formation of these symmetrically substituted salts is probably a consequence of a Mannich retroreaction, which takes place for the products of the addition of amines to α, β-unsaturated ketones; the resulting aldehyde, ketone, and amine then give the pyridinium salt via the scheme in [8, 9]. Dimedone monoanil and dianil were isolated as side products in the reaction of benzalacetophenone with aniline and dimedone in equimolar amounts.

The reaction takes place when mixtures of the components in xylene are refluxed. In contrast to the described synthesis of symmetrical salts from aldehydes, ketones, and amines [8, 9], in which the use of p-toluenesulfonic acid as the catalyst is compulsory, in the reaction under consideration the absence of a catalyst in a number of cases gives the same result as that obtained when a catalyst is used. However, the addition of p-toluene-sulfonic acid improves the results in the preparation of salts Im, n and when dimedone and malonodinitrile are used. The addition of acetic acid to the reaction mixture does not affect the results. An equimolar ratio of the α, β-unsaturated ketone, the amine, and the compound with a labile hydrogen atom was used in most cases. The use of an excess of one of the components does not increase the yield of the salt; the use of a threefold excess of benzalacetophenone makes it possible to sharply increase the yield of salt IIk only in the reaction of benzalacetophenone with aniline and dimedone, and dimedone monoanil and dianol were not detected.

The IR spectra of all of the pyridinium perchlorates obtained contain an intense band at ~1100 cm^{-1} (ClO_4^-), which is absent in the spectra of the chlorides. The stretching vibrations of the pyridinium structure show up in the form of bands at 1610-1620 cm^{-1}. In the spectrum of salt IIk the carbonyl group absorbs at 1696 cm^{-1}, as compared with 1710 cm^{-1} for salt IIl. In the spectra of salts Im, n the carboxy group gives bands at ~1705 cm^{-1} (C=O), as well as at 3372 cm^{-1} for Im and at 3455 cm^{-1} for In (OH). In the spectrum of salt IIc the OH group also absorbs at 3328 cm^{-1}. The spectra of salts IVa and Va, b contain an absorption band of a CN group at ~2220 cm^{-1} and a double band, which is characteristic for a primary amino group, at 3330 and 3470 cm^{-1}. Absorption bands of double bonds and functional groups are absent in the spectra of the remaining salts.

TABLE 1. PMR Spectra of the Pyridinium Salts

Compound	Chemical shifts, ppm, and intensities of the salts (assignment)[a]
Im	1,87 q, 2H[b]; 1,98 q, 2H[b]; 2,79 t, 2H (5-H); 3,08 t, 2H (8-H)
In	1,77 m, 2H[b]; 1,85 m, 2H[b]; 2,74 t, 2H (5-H); 3,15 t, 2H (8-H)
IIa	1,93 quint., 2H[b]; 2,03 q, 2H[b]; 2,81 t, 2H (5-H); 2,98 т, 2H (8-H)
IId	1,89 m, 4H (6-H, 7-H); 2,64 m, 2H (5-H); 3,10 m, 2H (8-H); 8,25 d, 1H (4-H)
IIf	1,33 s, 9H (tert-C_4H_9); 1,82 q, 2H[b], 1,92 q, 2H[б]; 2,52 t., 2H (5-H); 2,88t, 2H (8-H)
IIi	0,79 t, 3H (CH_3CH_2); 2,55 q, 2H (CH_2CH_3)
IIk	1,19 s, 6H (CH_3); 2,88 br.s., 2H[c]; 2,95 br.s, 2H[s]
IIl	1,10 s, 6H (CH_3); 1,80 q, 4H (6-H, 7-H); 2,64 m, 6Hd (5-H, 8-H); 2,82 br.s., 2H[d]
Va	1,76 q, 4H (6-H, 7-H); 2,45 m, 4H (5-H, 8-H); 8,45 br.s, 2H (NH_2)
Vb	1,74 m, 4H (6-H, 7-H); 2,40 m, 4H (5-H, 8-H); 4,00 s., 3H (OCH_3); 8,45br.s, 2H (NH_2)

[a]The atoms of the acridine structure are numbered in salt IIl, whereas the atoms of the quinoline structure are numbered in the remaining salts, except for IIi. [b]Due to 6-H or 7-H. [c]Due to 6-H or 8-H. [d]Due to 2-H or 4-H.

In the PMR spectra (Table 1) of tetrahydroquinolinium salts Im, n and IIa, d, f the signals of the 5-H and 8-H protons, which are adjacent to the pyridinium ring, usually show up in the form of triplets (2H) at, respectively, 2.5-2.8 ppm and 2.9-3.1 ppm; the signals of the 6-H and 7-H protons, which are remote from the pyridinium ring, show up at 1.75-2.05 ppm, either in the form of closely located quintets (2H each) or in the form of an overall multiplet (4H). The signals of the protons of the cyclohexene fragment of 2-ketooctahydroacridinium salt IIl give a similar pattern. The signals of the methylene groups of the ketocyclohexene ("dimedone") fragment of salts IIk, l show up in the form of slightly broadened singlets; in conjunction with the equivalence of the CH_3 groups (which give an overall singlet), this may indicate the planar structure of this fragment. The spectrum of monocyclic salt IIi contains signals of a C_2H_5 group bonded to the pyridinium ring; this ecludes the alternative structure of a 2-benzyl-3-methyl-1,4,6-triphenylpyridinium salt. The spectrum of 4-unsubstituted salt IId contains a doublet of a 4-H proton at 9.25 ppm; this doublet is absent in the spectra of the other salts. In addition to the signals presented in Table 1, the spectra of chlorides Im, n contain signals of solvate-bonded ethanol in the form of a triplet at 1.18 ppm, a quartet at 3.59 ppm, and a broad signal at 4.5 ppm.

Perchlorates IIa, d, f were also obtained by alternative synthesis from the corresponding 1,5-diketones and aniline in the presence of C_2Cl_6.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Specord IR-75 spectrometer. The PMR spectra of solutions in d_6-DMSO were obtained with Bruker HX-90E (90 MHz) and Bruker WM-250 (250 MHz) spectrometers with tetramethylsilane as the internal standard.

The characteristics of the synthesized salts are presented in Table 2.

Synthesis of the Pyridinium Salts. A) A mixture of 0.02 mole of the α, β-unsaturated ketone (0.06 mole in the case of salt IIk) or Mannich base IIIa (for salts IId, e), 0.02 mole of the amine, 0.02 mole of the ketone, malonodintrile or cyanoacetic ester, 0.03 mole of C_2Cl_6, and 50 ml of xylene (100 mg of p-toluenesulfonic acid was added in the synthesis of Im, n, IIk, l, IV, and V) was refluxed with a Dean—Stark trap for 5-7 h until the liberation of water ceased. The mixture was then cooled, and the xylene layer was decanted from the precipitated viscous oil. For the isolation of chlorides Imn, n the oil was triturated with 50 ml of ethanol, whereas the oil was triturated with 10 ml of acetone for the isolation of chloride IVa; the crystallized chlorides were removed by filtration. Chlorides Im, n were recrystallized from ethanol; the solvate-bonded ethanol was not removed when they were heated to 140°C (3 mm). Chloride IVa was reprecipitated from ethanol by means of diethyl ether.

For the isolation of the perchlorates the oil that precipitated during the reaction was refluxed with 100 ml of water, the aqueous layer was separated, and the operation was

TABLE 2. Characteristics of the Synthesized Pyridinium Salts

Compound	mp, deg C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
Im	210—212	72,8	6,3	3,0	$C_{31}H_{33}ClNO_{3,5} \times$ $\times 1,5\ C_2H_5OH$	72,8	6,5	2,7	33
In	300 (dec.)	72,8	6,0	2,8	$C_{29}H_{27}ClNO_{3,5} \times$ $\times 0,5\ C_2H_5OH$	72,4	5,6	2,9	49
IIa	211—213	70,2	5,3	2,9	$C_{27}H_{24}ClNO_4$	70,2	5,2	3,0	54
IIb	164—166	72,6	5,0	2,6	$C_{31}H_{26}ClNO_4$	72,6	5,1	2,7	8
IIc	196—198	67,4	4,9	3,3	$C_{27}H_{24}ClNO_5$	67,4	5,0	2,9	33
IId	170—172	65,7	5,4	3,5	$C_{21}H_{20}ClNO_4$	65,3	5,2	3,6	56
IIe	198—200	69,3	5,4	3,2	$C_{25}H_{22}ClNO_4$	68,8	5,1	3,2	28
IIf	238—239	68,2	6,3	3,2	$C_{25}H_{28}ClNO_4$	68,0	6,3	3,2	17
IIg	119—121	70,2	5,3	3,4	$C_{26}H_{22}ClNO_4$	69,9	4,9	3,1	27
IIh	171—173	65,8	3,9	5,2	$C_{29}H_{21}ClN_2O_6$	65,8	4,0	5,3	30
IIi	155—157	72,6	5,4	2,7	$C_{31}H_{26}ClNO_4$	72,7	5,1	2,7	28
IIk	267—268	69,4	5,6	2,9	$C_{29}H_{26}ClNO_5$	69,1	5,1	2,8	60
IIl	280—282	66,8	6,2	2,9	$C_{27}H_{28}ClNO_5$	67,3	5,8	2,9	29
IVa	245—247	72,7	6,0	11,7	$C_{22}H_{20}ClN_3$	73,0	5,5	11,6	10
Vb	243—246	61,6	4,9	9,8	$C_{22}H_{20}ClN_3O_4$	62,0	4,7	9,4	17
Vb	282—283	60,1	5,1	8,9	$C_{23}H_{22}ClN_3O_5$	60,5	4,8	9,2	18

repeated two more times. The combined aqueous extract was cooled, 5 ml of 25% ammonium hydroxide was added, and the mixture was extracted with ether four times. A saturated solution of NH_4ClO_4 was added dropwise with stirring to the clear aqueous layer, and the precipitated perchlorate was removed by filtration. In the reaction of benxalcyclohexanone with cyanoacetic ester and aniline the isolated perchlorate was salt IIj (20% yield), whereas salt VII (5% yield) was isolated in the reaction of benxalacetophenone with malonodinitrile and aniline. Mixtures of these perchlorates with perchlorates IIj and VI, respectively, were formed in the synthesis of salts Va, b. For separation, the mixtures were treated with chloroform, in which salts Va and Vb are insoluble. Salts IIj and VI were obtained in 20% and 24% yields, respectively. Salts IIj, VI, and VII were identical to genuine samples with respect to their IR spectra.

Perchlorate Va was obtained by the addition of NH_4ClO_4 to an aqueous solution of chloride IVa.

The perchlorates were recrystallized: IIb, d, e from propanol, IIi from dioxane, IIc from dioxane—water (2:3), and the remaining perchlorates from ethanol.

B) A mixture of 0.02 mole of IIIb, 0.02 mole of cyclohexanone or malonodinitrile, 0.03 mole of C_2Cl_6, 100 mg of p-toluenesulfonic acid, and 50 ml of xylene was treated as in variant A. Workup gave salt IIj (identical to a genuine sample) in 44% yield or IIl (identical to the product obtained by means of variant A) in 7% yield.

C) A mixture of 0.02 mole of the corresponding 1,5-diketone, 0.02 mole of aniline, 0.03 mole of C_2Cl_6, 50 mg of p-toluenesulfonic acid, and 40 ml of xylene was refluxed with water separation for 4 h until the liberation of water ceased, after which it was worked up as in variant A. Perchlorates IIa, IId, and IIf were obtained in 50%, 77%, and 64% yields, respectively. The compounds were identical (according to the IR spectra) to the corresponding samples obtained by means of variant A.

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SYNTHESIS OF N-(8-METHOXY-5-QUINOLYLSULFONYL)AZIRIDINE AND ITS REACTIONS WITH SECONDARY AMINES. PMR SPECTRA AND STRUCTURES OF THE DERIVATIVES OBTAINED

I. N. Gracheva, E. P. Prokof'ev, I. R. Kovel'man,
and A. I. Tochilkin

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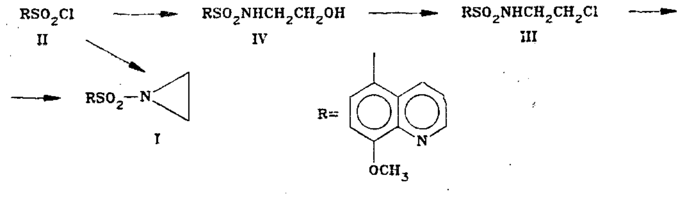
A method for the synthesis of a new fluorescent derivative of ethyleneimine, viz., N-(8-methoxy-5-quinolylsulfonyl)-aziridine, starting from 8-methoxyquinoline-5-sulfonyl chloride was developed. The quinolylsulfonylaziridine reacts smoothly with secondary aliphatic amines to give 8-methoxy-5-[N-(2-N-dialkylethylamino)] quinolinesulfonamides. In a study of the PMR spectra of these compounds it was established that significant deshielding of the 4-H proton (0.8 ppm) and a substantial increase (by 0.8 ppm) in $^3J_{(6,7)}$ are characteristic signs of the introduction of aziridinylsulfonyl or N-(2-N-dialkylamino)sulfonamido substituents into the 5 position of 8-methoxyquinoline.

N-Sulfonylaziridines are activated alkylating compounds that react readily with nucleophilic groups [1]. The reactions of N-sulfonylaziridines can be used as a mild method for the introduction of sulfonamidoethyl groups into organic compounds [2].

N-Sulfonylaziridines of the quinoline series could be used as fluorescent probes for the study of the structures of proteins and enzymes and as analytical reagents for amino and sulfhydryl groups in analog with 1-dimethylamino-5-naphthylsulfonylaziridine (dansylaziridine) [3] and 1-dimethylamino-naphthalene-5-sulfonyl chloride (dansyl chloride) [4].

In the present paper we report the synthesis and reactions with secondary amines of N-(8-methoxy-5-quinolylsulfonyl)aziridine (I), which was obtained on the basis of the previously described 8-methoxyquinoline-5-sulfonyl chloride (II), which is a highly sensitive, photostable, fluorescent reagent for amines, amino acids, and peptides [5].



Like other arylsulfonyl derivatives of ethyleneimine, quinolylsulfonylaziridine I is formed in good yield by the reaction of sulfonyl chloride II with ethyleneimine in chloroform [2] or by cyclization of 8-methoxy-5-[N-(2-chloroethyl)]quinoline-sulfonamide (III) under the conditions of the Gabriel reaction in aqueous acetone or methanol in the presence of KOH or NaOH [6]. Chloroethyl derivative III is synthesized by treatment of 8-methoxy-5-[N-(2-hydroxyethyl)]quinolinesulfonamide (IV), obtained by the reaction of sulfonyl chloride

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