ACID-CATALYZED ACYLATION OF 4-ALKYL-3-AZAPYRYLIUM SALTS AND THE SYNTHESIS OF 4-ACYLAMINOPYRYLIUM SALTS

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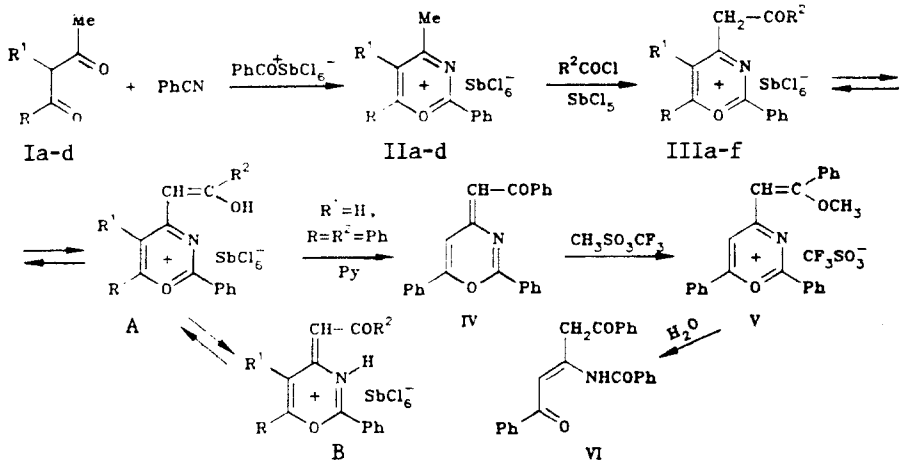
4-Alkyl-3-azapyrylium salts undergo acylation at the alkyl group under acid-catalyzed conditions to give 4-acylmethyl-3-azapyrylium derivatives, which upon heating in proton-donating solvents recyclize to give 4-acylaminopyrylium salts.

We have previously reported the preparation of 3-azapyrylium salts from 1,3-diketones, benzonitrile, Ac_2O, and $HClO_4$. In studying the properties of these newly synthesized compounds we have found that 3-azapyrylium hexachloroantimonate salts II, which can be prepared analogously to the perchlorates by replacement of the $Ac_2O/HClO_4$ mixture by benzoyl hexachloroantimonate, react with acyl chlorides in the presence of $SbCl_5$ to give 4-acylmethyl-3-azapyrylium salts III; the behavior of the latter salts is similar to that of other acylmethylazines [2], namely, they can exist in equilibrium with their enol A or ylidene B isomers.



I, II a $R=C_6H_5$, $R^1=H$; b $R=CH_3$, $R^1=H$; c $R=t\text{-}C_4H_9$, $R^1=H$; d $R=C_6H_5$, $R^1=CH_3$;
III a $R=R^2=C_6H_5$, $R^1=H$; b $R=C_6H_5$, $R^1=H$, $R^2=CH_3$; c $R=CH_3$, $R^1=H$, $R^2=C_6H_5$;
d $R=R^2=CH_3$, $R^1=H$; e $R=t\text{-}C_4H_9$, $R^1=H$, $R^2=C_6H_5$; f $R=R^2=C_6H_5$, $R^1=CH_3$

The PMR spectra of compounds III (Table 1) do not contain a resonance signal for the CH_2 group; two one-proton singlets are observed, however, in the 6.20-7.50 ppm region, which may be assigned to the CH protons in the A or B isomers. The quantitative concentration of the enol and ylidene isomers can be determined only by ^{14}N- and ^{17}O-NMR spectroscopy [2]. In order to obtain a qualitative estimate of the position of tautomeric equilibrium in this case we have prepared two model compounds V and VII, which are analogous to isomer A in that they contain a C=C bond in conjugation with the 3-azapyrylium cation.

Trifluoromethanesulfonate V was synthesized by methylation of 1,3-oxazine IV, itself prepared from hexachloroantimonate IIIa by deprotonation with pyridine. That alkylation of 1,3-oxazine IV occurred at the carbonyl group was confirmed by hydrolysis of the product V to give diketone VI. The second model compound was synthesized by condensation of salt IIa with benzaldehyde (see scheme on page 221).

Comparison of the electronic absorption spectra of hexachloroantimonates IIIa and VII supports the presence of a C=C bond in conjugation with the 3-azapyrylium cation in the acylation product IIIa, based on the fact that

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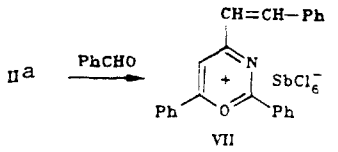
TABLE 1. Physical Characteristics of Newly Synthesized Compounds

Compound*	Molecular formula	mp, °C (dec.)	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm**	Yield, %
IIa	$C_{17}H_{14}Cl_6NOSb$	170...171	1620, 1593	3,18 (3H, s, 4-CH_3)	61
IIb	$C_{12}H_{12}Cl_6NOSb$	155...156	1619, 1592	3,08 (3H, s 4-CH_3); 3,28 (3H, s, 6-CH_3)	34
IIc	$C_{15}H_{18}Cl_6NOSb$	160...161	1609, 1573	1,65 (9H, s —$C(CH_3)_3$); 3,13 (3H, s, 4-CH_3)	44
IId	$C_{18}H_{16}Cl_6NOSb$	152...155	1595, 1562	2,77 (3H, s, 5-CH_3); 3,11 (3H, s, 4-CH_3); 7,40...8,60 (10H, m Ar—H)	25
IIIa	$C_{24}H_{18}Cl_6NO_2Sb$	155...160	1645, 1570	—	85
IIIb	$C_{19}H_{16}Cl_6NO_2Sb$	147...150	1645, 1625, 1570	2,45 (3H, s,CH_3CO); 6,25 (1H,s, CH); 7,49 (1H, s, CH); 7,55..., 8,70 (10H, m, Ar—H)	71
IIIc	$C_{19}H_{16}Cl_6NO_2Sb$	159...161	1658, 1600, 1580	2,68 (3H, s, 6-CH_3); 6,80 (1H, s, CH); 7,05 (1H, s, CH); 7,53... 8,48 (10H, m, Ar—H)	75
IIId	$C_{14}H_{14}Cl_6NO_2Sb$	150...152	1660, 1582	2,38 (3H, s, CH_3CO); 2,79 (3H, s, 6-CH_3); 6,16 (1H, s, CH)	66
IIIe	$C_{22}H_{22}Cl_6NO_2Sb$	190...191	1650, 1580	—	67
IIIf	$C_{25}H_{20}Cl_6NO_2Sb$	186...188	1636, 1567	2,56 (3H, s,5-CH_3); 6,90 (1H, s, CH); 7,30...8,65 (15H, m, Ar—H)	72
VIII	$C_{19}H_{16}ClNO_4$	218...219	1645, 1587, 1573	2,05 (3H,s, CH_3CO); 5,78 (1H, s, CH); 6,88 (1H, s, CH); 7,0... 8,0 (10H, m, Ar—H)	32
Xa	$C_{19}H_{16}ClNO_6$	216...217	3250, 1722, 1640	2,45 (3H, s, 2-CH_3); 6,95...7,90 (11H,m, Ar—H и 3-H); 8,28 (1H, s, 5-H); 9,73 (1H, s, NH)	31
Xb	$C_{14}H_{14}ClNO_6$	245...247	3280, 1750, 1640	2,08 (3H, s, CH_3CO); 2,46 (3H, s, 2-CH_3); 7,08...7,88 (6H, m, Ar—H m, 3-H); 8,10 (1H, s, 5-H); 9,60 (1H, s, NH)	51
Xc	$C_{15}H_{16}ClNO_6$	222...223	3380, 1745, 1620	2,03 (3H, s, CH_3CO); 2,15 (3H, s, 3-CH_3); 2,48 (3H, s, 2-CH_3); 7,08...7,83 (5H, Ar—H); 8,88 (1H, s, 5-H); 9,85 (1H, s, NH)	29
Xd	$C_{16}H_{18}ClNO_6$	226...227	3300, 1735, 1628	1,13 (3H, t, J=7 Hz, 2-$CH_2\mathbf{CH_3}$); 2,05 (3H, s, CH_3CO); 2,16 (3H, s, 3-CH_3); 2,89 (2H, q, J=7 Hz 2-$\mathbf{CH_2}CH_3$); 7,0...7,85 (5H, m,	37
Xe	$C_{15}H_{16}ClNO_6$	186...187	3250, 1750, 1638	,09 (3H, t, J=7 Hz 2-$CH_2\mathbf{CH_3}$); 2,20 (3H, s, CH_3CO); 2,76 (2H, Ar—H); 8,95 (1H, s, 5-H); 9,8 (1H, s, NH) q, J=7 Hz, 2-$\mathbf{CH_2}CH_3$); 7,0...7,83 (6H, m, Ar—H 3-H); 8,14 (1H, s, 5-H); 9,50 (1H, s, NH)	45
XIa	$C_{19}H_{16}Cl_6NO_2Sb$	180...182	3380, 1721, 1640	—	27
XIb	$C_{14}H_{14}Cl_6NO_2Sb$	175...179	3350, 1718, 1642	2,76 (6H, s, 2- 6-CH_3); 7,50...8,15 (7H, m, Ar—H 3-H, 5-H); 9,93 (1H, s, NH)	50
XIc	$C_{22}H_{22}Cl_6NO_2Sb$	231...232	3340, 1718, 1632	—	14

*UV spectrum of compound IIIa (in dichloroethane), λ_{max}, nm (log ε): 445 (4.75), 467 (4.90).

**The spectra of compounds IIa-c, IId were taken in nitrobenzene; IId, IIIf in nitrobenzene-D_5; IIIb, c, XIb in nitromethane; and VIII, Xa-e in CF_3COOH.

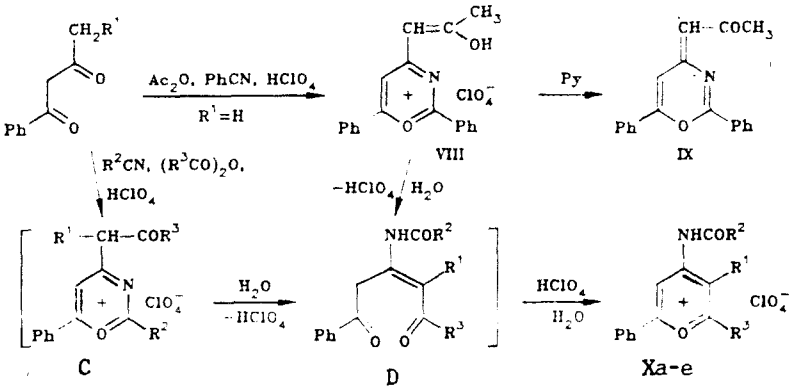


VII

the long-wavelength absorption bands in salts IIIa and VII are practically the same in position and form, and similar in intensity.

The IR spectra of compounds V and VII exhibit a medium-intensity band in the 1630-1645 cm^{-1} region which may be attributed to the stretching vibration of an exocyclic C=C bond. The same type of band is also observed in the IR spectra of salts III. Based on their UV and IR spectral data, we conclude that hexachloroantimonates III exist predominantly in their enol form A.

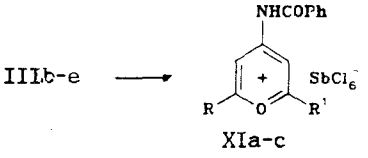
By varying the conditions for the reactions of 1,3-diketones with nitriles and carboxylic acid anhydrides in the presence of $HClO_4$ we have found that 3-azapyrylium salt formation and acylation reactions can be carried out in one step. Thus, heating a mixture of benzoylacetone, benzonitrile, Ac_2O, and 70% $HClO_4$ gave perchlorate VIII, which was converted to 1,3-oxazine IX by deprotonation with pyridine. According to its PMR and IR spectral data, salt VIII also exists in its enol form, analogous to hexachloroantimonate IIIb.



C D Xa-e

X a $R^1=H$, $R^2=C_6H_5$, $R^3=CH_3$; b $R^1=H$, $R^2=R^3=CH_3$; c $R^1=R^2=R^3=CH_3$; d $R^1=R^2=CH_3$, $R^3=C_2H_5$; e $R^1=H$, $R^2=CH_3$, $R^3=C_2H_5$

Determination of the structure of the other acylation products C is complicated by the fact that they are readily converted to 4-acylaminopyrylium salts Xa-e upon exposure to moist air. This transformation is accelerated upon heating perchlorates C in ethanol. Hexachloroantimonates III also undergo recyclization upon heating in ethanol or acetic acid, to give 4-benzoylaminopyrylium salts XI.

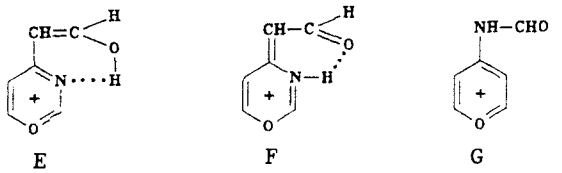


XIa-c

XI a $R=C_6H_5$, $R^1=CH_3$; b $R=R^1=CH_3$; c $R=C_6H_5$, $R^1=t\text{-}C_4H_9$

The rearrangements reactions described above involve hydrolytic cleavage of the 3-azapyrylium ring and subsequent cyclization of a 1,5-diketone intermediate D to generate a pyrylium salt. This was confirmed by isolation of 1,5-diketone VI upon refluxing hexachloroantimonate IIIa in ethanol.

The observed recyclization transformation is probably due to the greater thermodynamic stability of the final products. In order to verify this hypothesis we have carried out AM 1 calculations [3], with complete optimization of the geometric parameters, for the enol E and ylidene F isomers of the 4-formyl-3-azapyrylium cation, and for the 4-formylaminopyrylium cation G as well.



E F G

ΔH_f 578,6 (E), 597,0 (F), 527,1 kJ/mole (G)

The lower observed heat of formation for cation G compared to its isomeric structures E and F supports our conclusion, stated above, that the recyclization reaction of 4-acylmethyl-3-azapyrylium salts to 4-acylaminopyrylium salts is under thermodynamic control. The calculations also reveal that isomer E is more stable than isomer F by 18.4 kJ/mole. This result explains the preferential existence of products III in their enol forms.

In conclusion, we have demonstrated the acylation reaction of 4-alkyl substituted 3-azapyrylium salts; this reaction, in conjunction with subsequent recyclization of the resulting reaction products, has enabled us to develop a convenient method for the preparation of otherwise difficultly accessible 4-acylaminopyrylium salts.

EXPERIMENTAL

IR spectra were recorded using Vaseline mulls on a Specord IR 75 spectrophotometer; PMR spectra were obtained on a Tesla BS 487 S (80 MHz) spectrometer versus HMDS as internal standard. UV spectra were measured on a specord UV-vis spectrophotometer in dichloroethane solution. Mass spectra were recorded on a Finnigan 4021 spectrometer at an ionizing electron energy of 70 eV and at an ionization chamber temperature of 250°C. The physical characteristics of compounds IIa-d, IIIa-f, VIII, Xa-e, and XIa are summarized in Table 1.

The results of C, H, Cl, and N elemental analysis agreed with calculations.

AM 1 quantum mechanical calculations were carried out using a literature program [3], involving up to 75 AO, on a BESM-6 computer.

4-Methyl-2-phenyl-5R^1-6R-3-azapyrylium Hexachloroantimonates (IIa-d). To a cooled solution of 1.55 g (11 mmoles) benzoyl chloride in 7 ml nitromethane at −10°C was added sequentially 3 g (10 mmoles) $SbCl_5$, 10 mmoles 1,3-diketone Ia-d, and 2.5 ml benzonitrile. After 40 min the resulting precipitate was removed by filtration and washed with chloroform and ether.

2-Phenyl-4-acylmethyl-5R^1-6R-3-azapyrylium Hexachloroantimonates (IIIa-f). To a solution of 20 mmoles acyl chloride in 10 ml nitromethane was added 0.3 g (1 mmole) $SbCl_5$ and 10 mmoles 3-azapyrylium hexachloroantimonate IIa-d. The reaction mixture was maintained at 20°C for several days, or heated for 10-15 min at 90°C. Upon cooling a precipitate appeared, which was filtered, washed with chloroform and ether, and recrystallized from nitromethane.

2,6-Diphenyl-4-benzoylmethylane-1,3-oxazine (IV, $C_{24}H_{17}NO_2$). A suspension of 3.0 g (4.37 mmoles) salt IIIa in 10 ml pyridine was heated at 70°C, cooled, and diluted with 100 ml ether. The filtrate was separated, evaporated under vacuum, and the residue recrystallized from benzene. mp 187-188°C. IR spectrum: 1650 (C=O); 1625 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 6.72 (1H, s, =CH); 7.15-8.30 (15H, m, Ar—H); 8.40 ppm (1H, s, =CH). Yield 11 g (72%).

2,6-Diphenyl-4-(β-methoxystyryl)-3-azapyrylium Trifluoromethanesulfonate (V, $C_{26}H_{20}F_3NO_5S$). To a suspension of 1.7 g (4.8 mmoles) oxazine IV in 15 ml dichloroethane was added 1.64 g (10 mmoles) methyl trifluoromethanesulfonate, and the mixture was heated to boiling. After 2 days the resulting precipitate was removed by filtration and recrystallized from nitromethane. mp 230-231°C. IR spectrum: 1640 cm^{-1} (C=C). PMR spectrum ($PhNO_2$): 4.30 ppm (3H, s, OCH_3). Yield 2.1 g (84%).

1,5-Diphenyl-3-(N-benzoylamino)-2-pentene-1,5-dione (VI, $C_{24}H_{19}NO_3$). **A.** A suspension of 1.0 g (1.94 mmoles) salt V in 20 ml ethanol was heated at reflux, cooled, and the resulting precipitate removed by filtration, mp 205-206°C (from nitromethane). IR spectrum: 1690 (C=O), 1630 cm^{-1} (NH—CO). PMR spectrum (DMF-D_7): 4.72 (2H, s, CH_2); 6.53 (1H, s, CH); 7.25-8.18 (15H, m, Ar—H); 13.66 ppm (1H, s, NH). Yield 0.65 g (90%).

B. Compound VI was prepared analogously from salt IIIa; mp 205-206°C. Yield 77%.

2,6-Diphenyl-4-styryl-3-azapyrylium Hexachloroantimonate (VII, $C_{24}H_{18}C_6NOSb$). A mixture of 2.6 g (4.46 mmoles) salt IIa, 10 ml nitromethane, and 0.6 g (5.7 mmoles) benzaldehyde was refluxed for 20 min, cooled, and the resulting precipitate removed by filtration. mp 203°C (decomp.) IR spectrum: 1632 cm^{-1} (C=C). Uf spectrum (in dichloroethane), λ_{max}, nm ($\log \varepsilon$): 413 (4.54), 470 (4.92). Yield 2.1 g (70%).

2,6-Diphenyl-4-acetonyl-3-azapyrylium Perchlorate (VIII, $C_{19}H_{16}ClNO_6$). To 7.0 g (68 mmoles) acetic anhydride cooled to 0°C was added sequentially 1 ml (10 mmoles) 70% $HClO_4$, 3.1 g (30 mmoles) benzonitrile, and 1.62 g (10 mmoles) benzoylacetone. The reaction mixture was heated to the onset of boiling (~5 min), and cooled. The resulting precipitate was separated by filtration, and washed with chloroform and ether.

2,6-Diphenyl-4-acylmethylene-1,3-oxazine (IX, $C_{19}H_{15}NO_2$). Salt VIII (1.0 g, 2.56 mmoles) was dissolved in 5 ml pyridine and after 2 min 50 ml ether was added. The resulting precipitate was separated by filtration, and the filtrate evaporated. The residue was recrystallized from hexane—benzene (2:1); mp 134-135°C. IR spectrum: 1660 (C=C); 1626 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 2.60 (3H, s, CH_3); 5.40 (1H, s, =CH); 6.24 (1H, s, =CH); 7.25-

8.25 ppm (10H, m, Ar—H). Mass spectrum, m/e (I_{rel}, %): 289 (28.8), 274 (56.6), 246 (9.5), 212 (5.7), 184 (14.9), 105 (100). Yield 0.45 g (61%).

4-Acylaminopyrylium Perchlorates (Xa-e). To 7.0 g (68 mmoles) acetic anhydride cooled to 0°C was added sequentially 1 ml (10 mmoles) 70% $HClO_4$, 10 mmoles 1,3-diketone, and 40 mmoles nitrile. The reaction mixture was heated to the onset of boiling (5 min), and cooled. The resulting precipitate was separated by filtration and recrystallized from ethanol.

4-Benzoylaminopyrylium Hexachloroantimonates (XIa-c). A mixture of 5 mmoles salt IIIb-e, 15 ml acetic acid, and 3 ml nitromethane was boiled for 3 min, cooled, and after 1 h 200 ml ether was added. The resulting precipitate was separated by filtration and recrystallized from acetic acid.

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REACTIONS OF BENZOTHIAZOLE-2-THIONE AND BENZOTHIAZOLE-2-ONE WITH ACETYLENE

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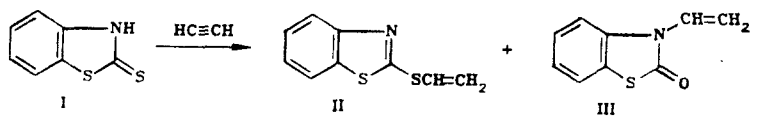
Reaction of benzothiazole-2-thione and benzothiazole-2-one with acetylene in the presence of potassium hydroxide or cadmium acetate gives 2-vinylthiobenzothiazole and 3-vinylbenzothiazol-2-one, respectively. Benzothiazole-2-thione is partially converted to benzothiazol-2-one by the action of $Cd(OAc)_2$. Under vinylation conditions the latter also forms 2-vinylthioaniline.

The reaction of benzothiazole-2-thione (I) with acetylene under alkaline catalytic conditions has been reported to give only 2-vinylthiobenzothiazole (II) [1]. In this work we have studied the reaction of thione I with acetylene in the presence of $Cd(OAc)_2$, which is effective in catalyzing the vinylation of azolethiones [2] and azolones [3]. Standard conditions for this reaction [20% $Cd(OAc)_2$, 180°C, 3 h] gives the basic product II together with a small amount (≈10%) of 3-vinylbenzothiazol-2-one (III). The yield of III was not affected by raising the reaction temperature or increasing the amount of catalyst.



I II III

The appearance of III may be due either to substitution of the exocyclic sulfur atom for oxygen in thione I or scission of the 2-thiovinyl group from II to give benzothiazol-2-one (IV) with subsequent vinylation. At first sight, the second of these is the more likely since side chain splitting is a characteristic reaction of azolylvinylsulfides [4]. We have found that azolone IV is formed by heating thione I with $Cd(OAc)_2$. Compound II is stable toward cadmium acetate.

Interesting results were obtained for the reaction of azolone IV with acetylene. In the presence of KOH, vinylation occurs at the nitrogen atom to give the vinylketone III.

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