1,3-DIPOLAR CYCLOADDITION REACTIONS OF YLIDES FORMED FROM PYRIDINES AND DICHLOROCARBENE

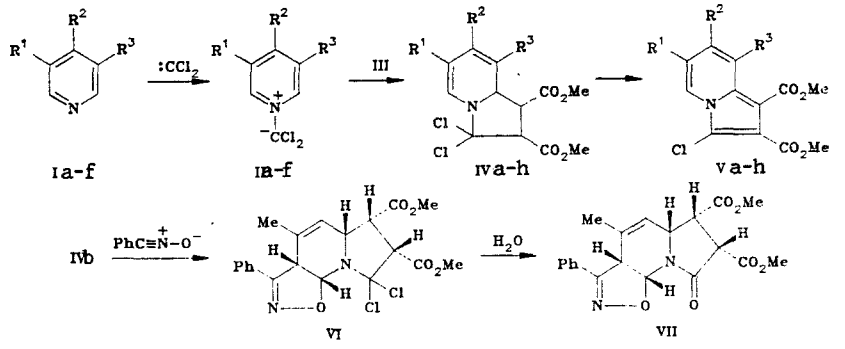
A. F. Khlebnikov, E. I. Kostik,
R. R. Kostikov, and V. Ya. Bespalov

UDC 547.821.2'821.441'831.1'834.
2.07:543.51'422.25:541.63

Pyridinium dichloromethylides, generated from substituted pyridines and dichlorocarbene, react endo-stereoselectively with dimethyl maleate to give substituted 3,3-dichloro-1,2,3,8a-tetrahydroindolizine-1,2-dicarboxylic acid dimethyl esters; the latter compounds are readily dehydrochlorinated and dehydrogenated to give the corresponding indolizine derivatives. Reaction of 3-substituted pyridines with dichlorocarbene and dimethyl maleate leads predominantly to the formation of 8-substituted indolizines. Cycloaddition of 4-picolinium dichloromethylide to unsymmetrical dipolarophiles occurs regioselectively. The observed selectivity in these reactions is consistent with predictions made on the basis of PMO theory.

Reaction of pyridine, 4-picoline, and quinoline with dichlorocarbene results in the formation of the corresponding cycloimmonium ylides, which undergo cycloaddition reactions with but-2-enedioic acid esters to give 3-chloroindolizine derivatives [1].

In the present paper we have studied the reactions of 3- and 4-substituted pyridines (I) and isoquinoline with dichlorocarbene in the presence of dipolarophiles, and have also investigated the stereo- and regioselectivity of the cycloaddition reactions of pyridinium dichloromethylides (II). Dichlorocarbene was generated via the reaction of chloroform with sodium hydroxide powder, or by thermal decomposition of sodium trichloroacetate; in both cases benzyltriethylammonium chloride was used as a phase transfer catalyst. The structures of the reaction products were established using spectral methods (Table 1) and by their chemical reactions (behavior). Reaction of substituted pyridines Ia-f with dichlorocarbene in the presence of dimethyl maleate II gave the tetrahydroindolizines IVa-h, which were detected by GLC and TLC analysis. Attempts to isolate compounds IVa-h by concentration of solutions obtained from column chromatography of the reaction mixtures led to resin formation and partial conversion of the compounds to substituted indolizines Va-h. The intermediate tetrahydroindolizine IVb was isolated in the form of its adduct with benzonitrile oxide, compound VI [2].



I—V a $R^1=R^2=R^3=H$; b $R^1=R^3=H$, $R^2=Me$; c $R^1=R^3=H$, $R^2=Cl$; d $R^1=R^3=H$, $R^2=PhCO$; e $R^1=R^2=H$, $R^3=Me$; f $R^1=R^2=H$, $R^3=Br$; g $R^1=Me$, $R^2=R^3=H$; h $R^1=Br$, $R^2=R^3=H$

Leningrad State University, Leningrad. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 355-362, March, 1990. Original article submitted July 13, 1988.

 0009-3122/90/2603-0304 $12.50

TABLE 1. Spectral Characteristics of New Compounds

Compound	IR spectrum (2% solution in $CHCl_3$), ν, cm^{-1}	PMR spectrum (10% solution in $CDCl_3$), δ, ppm (J, Hz)
Vc	1712, 1745	3,94 and 4,02 (s, MeO); 6,89 (d.d, 7,5, 2,1, 6-H); 8,00 (d.d 7,5, 0,9, 5-H); 8,18 (d.d, 2,1, 0,9, 8-H)
Vd	1718, 1743	3,85 and 3,99 (s, MeO); 7,47...7,80 (m, Ph); 7,81 (d.d, 7,5, 2,0, 6-H); 8,12 (d.d, 7,5, 1,0, 5-H); 8,58 (d.d, 2,0, 1,0 8-H)
Ve	1730	2,43 and 3,91 (s, MeO); 6,66 (m 6-H, 7-H); 7,87 (m, 5-H)
Vf	1736	3,91 and 3,95 (s, MeO); 6,59 (t 7,5, 6-H); 7,10 (d 7,5, 7-H); 7,98 (d 7,5, 5-H)
Vg	1705, 1740	2,30 (s, Me); 3,84 and 3,91 (s, MeO); 6,92 (d 10, 7-H); 7,80 (s, 5-H); 8,04 (d, 10, 8-H)
Vh	1715, 1743	3,80 and 3,88 (s, MeO); 7,15 (d.d, 10, 1,6, 7-H); 8,06 (d, 10, 8-H); 8,19 (m, 5-H)
VI	1750	1,56 (br.s, Me); 3,69 and 3,71 (s, MeO); 3,76 (d, 11,3, 7-H); 4,03 (t 11,3, 6-H); 4,12 (d, 8,5, 3a-H); 4,73 (br.d 11,3, 5a-H); 5,74 (br.s, 5-H); 6,40 (d 8,5, 9a-H); 7,35...7,69 (Ph)
VII	1740	1,59 (br.s Me); 3,73 and 3,83 (s, MeO); 3,81 (d, 5,4, 7-H); 3,89 (d.d, 8,0, 5,4, 6-H); 4,18 (d, 8,8, 3a-H); 4,68 (d.q. 8,0, 2,0, 5a-H); 5,67 (br.s 5-H); 6,60 (d, 8,8, 9a-H); 7,44 and 7,60 (m Ph)
VII*		1,10 (br.s Me); 3,14 and 3,26 (s MeO); 3,58 (d.d, 8, 5,3, 6-H); 3,83 (d, 5,3, 7-H); 4,50 (br.d, 8, 5a-H); 5,31 (br.s, 5-H); 6,56 (d, 9, 9a-H); 7,04 and 7,38 (m, Ph)
X		3,50 and 3,75 (s, MeO); 4,26 (d, 10, 1-H); 5,44 (d, 10, 10b-H); 5,72 (d, 7,5, 6-H); 6,79 (d 7,5, 5-H); 7,00...7,19 (m, arom)
XI	1731	3,95 and 4,02 (s MeO); 7,00 (d 7,5, 6-H); 7,53...7,74 (m, 7—9-H); 7,87 (d 7,5, 5-H); 8,43 (d.d 2,5, 5,5, 10-H)
XIII	1677, 1719, 1746	2,61 (s Me); 3,95 and 4,05 (s MeO); 7,73 (d 9,5, 6-H); 7,51...7,76 (m 2-H, 7—9-H); 8,27 (d 9,5, 5-H)
XV		1,82 (br.s, Me); 3,73 and 3,78 (s MeO); 3,94 (d 14, 1-H); 4,51 (br.d 14, 8a-H); 5,30 (s, 8-H); 5,34 (d, 8, 6-H); 6,74 (d 8, 5-H)
XV*		1,42 (br.s, Me); 3,25 (s 2-H); 3,35 and 3,39 (s, MeO); 3,77 (d 14, 1-H); 4,30 (br.d, 14, 8aH); 4,88 (d.d, 7,5, 1,5, 6-H); 4,92 (m, 1,5, 8-H); 6,29 (d, 7,5, 5-H)
XVII	1700, 1745	2,36 (s, Me); 3,91 (s 2 MeO); 6,54 (d.d, 7,0, 1,7, 6-H); 7,50 (s, 3-H); 7,76 (d, 7,0, 5-H); 7,86 (m, 8-H)
XIX	2223, 2233, 2247	2,41 (s, Me); 6,75 (d.d, 7,5, 1,7, 6-H); 7,45 (m, 8-H); 7,67 (s, 3-H); 7,93 (d, 7,5, 5-H)
XX	2220, 2248	2,42 (s, Me); 6,70 (s 2-H); 6,87 (d.d, 7,5, 1,7, 6-H); 7,33 (m 8-H); 8,13 (d 7,5, 5-H)
XXII	1696	6,75 (d.d 7,5, 1,8, 6-H); 7,43 (s, Ph); 8,07 (d 7,5, 5-H); 8,13 (m 8-H)
XXV	1730, 2258	1,57 (s, Me); 2,20 (d 4,0, 7b-H); 2,80 (d 11,5, 6-H); 2,82, (d 8,5, 6-H); 3,43 (d.d.d, 11,5, 8,5, 10,0, 7-H); 4,05 (d.d 10,0, 4,0, 7a-H); 5,27 (d 8,0, 2-H); 6,86 (d, 8,0, 3-H)
XXVI	1730, 2259	1,55 (s, Me); 1,82 (d.d, 3, 1, 7b-H); 2,86 (d 9, 6-H); 3,65 (d.t, 6, 9, 7-H); 4,13 (d.d, 6, 3, 7a-H); 5,26 (d 8, 2-H); 6,83 (d 8, 3-H)

*The PMR spectrum was taken in C_6D_6.

The spin-spin coupling constants (SSCC) for the 5a-H, 6-H, and 7-H protons indicate that compound VI and its hydrolysis product VII exist in the cis-configuration. The mass spectrum of compound VI contains a $[M-HCl]^{+\cdot}$ ion peak at m/e 402, while the mass spectrum of compound VII contains the molecular ion peak at m/e 384.

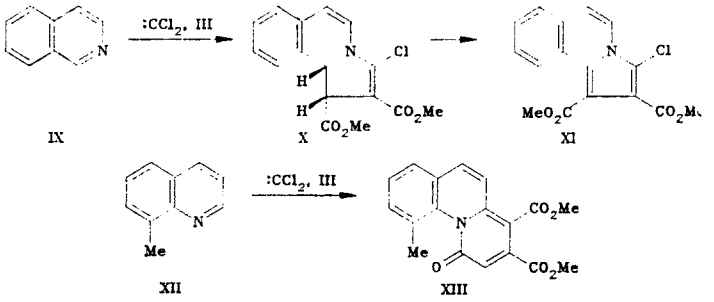
Upon treatment of compounds IVa-h with 2,3-dichloro-5,6-dicyanobenzoquinone or manganese dioxide the former compounds are converted quantitatively to indolizines Va-h (Table 1). The IR spectra of compounds Va-h contain C=O stretching vibration bands for the ester groups in the region 1700-1750 cm^{-1}. The signal assignments for the 5-H, 6-H, and 8-H protons in the PMR spectra of indolizines Va-d were made based on their chemical shift and SSCC values: $J_{56} = 7.5$; $J_{68} = 2$; $J_{58} = 1$ Hz. Comparison of the CS values for the 5-H protons in compounds Va-d (ca. 8.1 ppm) and the 3-R^1-7-R^2-indolizine-1,2-dicarboxylic acid dimethyl esters (VIIIa-d) (a R^1 = Me, R^2 = H, 5-H 7.69, 8-H 8.04 [3]; b R^1 = CN, R^2 = H, 5-H 8.28, 8-H 8.16 [3]; c R^1 = CO_2Me, R^2 = H, 5-H 9.48, 8-H 8.32 [4]; d R^1 = H, R^2 = PhCO, 5-H 7.98, 8-H 8.48 ppm [5]) confirms the presence of a chlorine atom in the $C_{(3)}$ position in indolizines Va-d, and not a CO_2Me group, since in the latter case a CS value of approximately 9.5 ppm would be expected for the 5-H proton.

In the case of the reactions of 3-substituted pyridines, Ie, f two isomeric indolizines are formed in each case, Ve, g and Vf, h, with the isomers having the substituent at the $C_{(8)}$ position predominating. The isomeric ratios for Ve and Vg (2.5:1) and Vf to Vh (2:1)

do not change during the course of reaction. In the PMR spectrum of indolizine Ve the 5-H, 6-H, and 7-H protons give rise to a degenerate ABX-type system, while the PMR spectrum of indolizine Vf contains two doublets for the 5-H and 7-H protons and a triplet for 6-H. The PMR spectra of the 6-substituted indolizines Vg, h contain a singlet for the 5-H proton and doublets for the 7-H and 8-H protons.

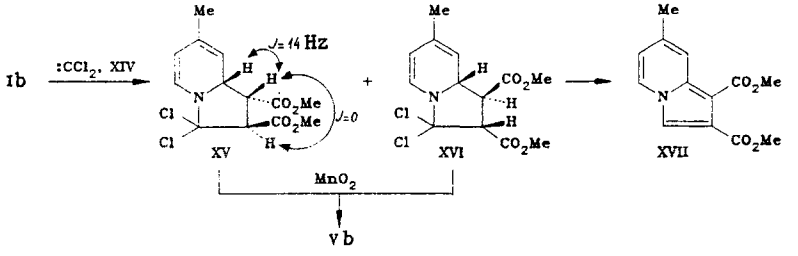
Reaction of 2-substituted pyridines with dichlorocarbene in the presence of dimethyl maleate does not lead to indolizine formation. Under these conditions 2-chloro- and 2-bromopyridine are practically unchanged during the reaction course, whereas 2-picoline undergoes resinification.

Reaction of isoquinoline IX with dichlorocarbene and dimethyl maleate leads to the formation of one of two possible structurally isomeric cycloaddition products of isoquinolinium dichloromethylide. Compound X was isolated from this reaction; it is the dehydrohalogenation product of the primary cycloadduct. The SSCC for the 1-H and 10-H protons (10 Hz) reveals that compound X has the cis-configuration. Upon reaction with oxidants compound X is converted quantitatively to the pyrroloisoquinoline XI.

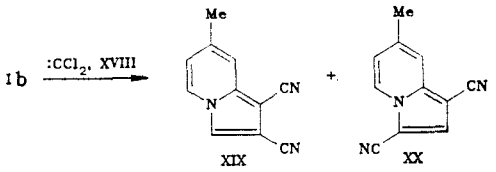


According to [1], quinoline reacts with dichlorocarbene and dimethyl maleate to form 1-chloropyrrolo[1,2-a]quinoline-2,3-dicarboxylic acid dimethyl ester. Under the same conditions 8-methylquinoline XII gave the dimethyl ester of 10-methyl-1-oxo-1H-pyrido[1,2-a]-quinoline-3,4-dicarboxylic acid (XIII) in 2% yield. The main amount of compound XII is recovered unchanged. The mass spectrum of compound XIII contains the molecular ion peak at m/e 325, and the IR spectrum contains bands corresponding to the C=O stretching vibrations of both the ester and amide functional groups (1746, 1719, 1688 cm^{-1}); the PMR spectrum exhibits singlets for the methyl and methoxyl group protons, doublets for the 5-H and 6-H protons, and multiplets for the remaining protons.

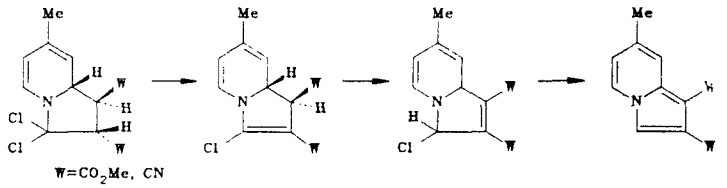
Substituted indolizines are also formed upon reaction of 4-picoline and dichlorocarbene with other dipolarophiles, such as dimethyl fumarate, fumarodinitrile, methyl 3-phenylpropiolate, and acrylonitrile. Reaction of 4-picoline with dichlorocarbene and dimethyl fumarate (XIV) leads to two stereoisomeric tetrahydroindolizines XV and XVI, which differ in their chromatographic parameters from tetrahydroindolizine IVb. It was possible to isolate tetrahydroindolizine XV by column chromatography, and based on its PMR spectrum it is assigned the 7-methyl-3,3-dichloro-1,2,3,t-8a-tetrahydroindolizine-r-1,t-2-dicarboxylic acid dimethyl ester structure; indolizine Vb and XVII, which did not contain chlorine, were also isolated. The yield of compound VII was increased upon addition of triethylamine to the reaction mixture. Upon treatment of the reaction mixture with manganese dioxide compounds XV and XVI were converted to indolizine Vb.



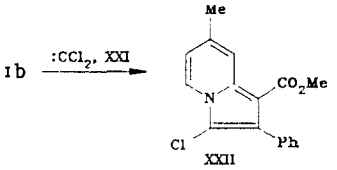
Reaction of 4-picoline with dichlorocarbene in the presence of fumaric acid dinitrile (XVIII) also gives two isomeric indolizines XIX and XX in a ca. 7:1 ratio.



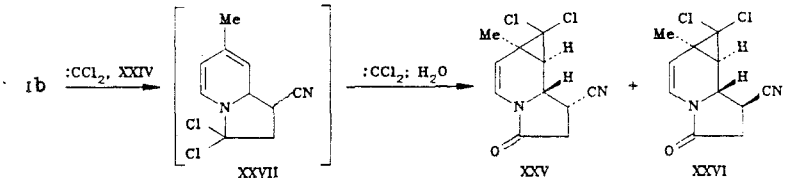
Formation of indolizines XVII and XIX, which do not contain chlorine, probably occurs via the following scheme:



Reaction of 4-picoline with dichlorocarbene and methyl 3-phenylpropiolate (XXI) gave the substituted indolizine XXII, whose structure was confirmed by comparison of its PMR spectrum with the PMR spectra of compounds Vb, VIIIa-d, and 1-R^2-3-R^1-7-methyl-2-phenylindolizines (XXIIIa, b) (a R^1 = OAc, R^2 = Ph, 8-H 7.1 [6]; b R^1 = H, R^2 = PhCO, 8-H 8.0 ppm [7]). The CS values for the 8-H protons in compounds XXII are in the same range as that for the 8-H proton in compound Vb, in which the 8-H proton is located adjacent to a CO_2Me group. However, the signal for the 8-H proton in compound XXIIIa, in which the proton is adjacent to a phenyl group, absorbs further upfield. The same product, although in lower yield, is formed when methyl cinnamate is used as the dipolarophile.



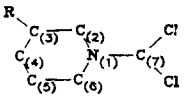
Reaction of 4-picoline with dichlorocarbene and acrylonitrile XXIV leads to the formation in 3% yield of two stereoisomeric 1a-methyl-1,1-dichloro-7-cyano-1a,7,7a,7b-tetrahydrocyclopropa[g]indolizin-5(6H)-ones (XXV, XXVI) in a 2:1 ratio. The low yield of indolizines in this reaction is due to the formation of a significant amount (34%) of 4,4,4-trichlorobutyronitrile, the addition product of trichloromethyl anion to acrylonitrile, as well as to polymerization of the latter. Configuration assignments were made based on the values of the SSCC for the 7-H, 7a-H, and 7b-H protons.



It has thus been shown that reaction of dichlorocarbene with substituted pyridines leads to the formation of the corresponding pyridinium dichloromethylides II, which undergo 1,3-dipolar cycloaddition reactions with electron deficient ethylene derivatives to give substituted 3,3-dichloro-1,2,3,8a-tetrahydroindolizines IV. Under the reaction conditions these compounds undergo partial, and in the presence of oxidants complete, dehydrochlorination and subsequent aromatization to give substituted indolizines V.

The primary adducts XXVII formed as the cycloaddition products of ylide IIb to acrylonitrile contain a multiple bond, which reacts readily with dichlorocarbene, resulting in the formation of cyclopropane derivatives, which can be further converted to the lactams XXV and XXVI. The configuration of the tetrahydroindolizine fragment in compounds VI and VII indicates that reaction of pyridinium ylide with dimethyl maleate results in the formation of an endo-cis(3+2)-cycloadduct. Reaction with dimethyl fumarate is also stereospecific, leading to the formation of two other possible stereoisomers. Upon reaction of 4-picolinium

TABLE 2. Quantum Mechanical Calculations Data for Pyridinium Dichloromethylides*[1]



Compound	R	MO*[2]	ε_i, eV	p_z AO coefficients and charges*[3]						
				1	2	3	4	5	6	7
IIa*[4]	H	ψ_{-1}	−0,65	−509	270	218	−472	218	270	508
		ψ_1	−7,65	−5	−393	60	406	60	−393	665
		ψ_2	−10,28	0	−526	472	0	472	526	0
		q	—	100	−97	8	−134	8	−97	−162
IIe	Me	ψ_{-1}	−0,64	−503	223	263	−477	176	309	503
		ψ_1	−7,63	−57	−390	60	406	60	−393	666
		ψ_2	−10,18	15	−531	−483	−37	435	509	16
		q	—	100	−80	−38	−118	6	−94	−165
IIi	Cl	ψ_{-1}	−0,94	−494	182	294	−476	153	325	509
		ψ_1	−7,90	56	−399	63	410	50	−397	656
		ψ_2	−10,40	24	−525	−474	−59	402	486	27
		q	—	99	−88	58	−122	14	−95	−146

*[1] Maleic acid: E_{LUMO} = −0.96, E_{HOMO} = −11.06 eV; c_i on the atoms in the C=C bond: LUMO ±0.580, HOMO 0.635.
*[2] ψ_{-1} LUMO, ψ_1 HOMO, ψ_2 OMO of the π-type, close to the HOMO, q atomic charge.
*[3] $c_i \times 10^3$ Coefficients, $q \times 10^3$ E charges.
*[4] Compound IIa is a planar molecule with bond lengths: $N_{(1)}$–$C_{(2)}$ 141.0; $C_{(2)}$–$C_{(3)}$ 139.6; $C_{(3)}$–$C_{(4)}$ 140.3; $N_{(1)}$–$C_{(7)}$ 135.7; 2-H–$C_{(2)}$ 109.0; 3-H–$C_{(3)}$ 109.2; 4-H-$C_{(4)}$ 108.8; $C_{(7)}$–Cl 172.9 nm; angles $C_{(2)}$–$N_{(1)}$–$C_{(6)}$ 117.5; $N_{(1)}$–$C_{(2)}$–$C_{(3)}$ 121.1; $N_{(1)}$–$C_{(7)}$–Cl 123.1; $C_{(2)}$–$C_{(3)}$–$C_{(4)}$ 121.1; 2-H–$C_{(2)}$–$N_{(1)}$ 118.2; 3-H–$C_{(3)}$–$C_{(2)}$ 118.4°.

dichloromethylide with unsymmetrical dipolarophiles only one regioisomer is obtained, in which the electron withdrawing substituent is located at the $C_{(1)}$ atom in the indolizine ring. Theoretical analysis of the cycloaddition process was carried out based on the results of electronic structure calculations of pyridinium dichloromethylides and maleic acid using MNDO [8]. According to these calculations, pyridinium dichloromethylide IIa adopts a planar configuration (cf. Table 2). Comparison of the electronic structure parameters of ylides and maleic acid reveals that the most important orbitals for cycloaddition interaction are the ylide HOMO and dipolarophile LUMO levels. MO calculations [9, 10] also suggest that in the case of an unsymmetrical dipolarophile with a multiple bond between atoms C' and C", the C' atom, which carries the electron withdrawing substituent, has a lower coefficient in the LUMO than the adjacent C" atom. Taking into account the HOMO coefficients for the $C_{(2)}$ and $C_{(7)}$ atoms in the ylide, we conclude that cycloaddition involving the formation of bonds between C'–$C_{(2)}$ and C"–$C_{(7)}$ should occur more readily than cycloaddition via C'–$C_{(7)}$ and C"–$C_{(2)}$ bond formation. This is consistent with the observed regioselectivity for the reaction of pyridinium dichloromethylide with phenylpropiolic acid ester or acrylonitrile.

Cycloaddition of unsymmetrical pyridinium ylides IIe, f to dimethyl maleate gives isomeric 8- and 6-substituted indolizines, with the former predominating. Analogous results were obtained upon reaction of 3-methyl- and 3-cyanopyridinium dicyanomethylides with dimethyl acetylenedicarboxylate. [11]. The observed cycloaddition selectivity cannot be explained in terms of steric factors. Using the results of quantum mechanical calculations (Table 2) according to [12], we have estimated the MO perturbation energies for reaction of ylides IIe, i with maleic acid. Interaction of the ψ_1 and ψ_2 MO levels of the ylide with the LUMO of maleic acid was considered. The estimated values of the perturbation energies for the formation of the 8-R-substituted indolizine isomer (R = Me, Cl) are equal to

TABLE 3. Melting Points and Molecular Formulas of New Compounds

Compound	mp, °C*	Molecular formula	Compound	mp, °C*	Molecular formula
Vc	124,5...125,5	$C_{12}H_9Cl_2NO_4$	X	95...97	—**
Vd	136,5...137	$C_{19}H_{14}ClNO_5$	XI	145,5...146,5	$C_{16}H_{12}ClNO_4$
Ve	66,5...67,5	$C_{13}H_{12}ClNO_4$	XIII	153...154	$C_{18}H_{15}NO_5$
Vf	146...147	$C_{12}H_9BrClNO_4$	XVII	69	$C_{13}H_{13}NO_4$
Vg	125,5...126	$C_{13}H_{12}ClNO_4$	XIX	201...202	$C_{11}H_7N_3$
Vh	119,5	$C_{12}H_9BrClNO_4$	XX	159...160	$C_{11}H_7N_3$
VI	190 (dec.)	$C_{20}H_{20}Cl_2N_2O_5$	XXII	163...164,5	$C_{17}H_{14}ClNO_2$
VII	109...110	—**	XXV	196....196,5	$C_{11}H_{10}Cl_2N_2O$
			XXVI	142,5	$C_{11}H_{10}Cl_2N_2O$

*Compounds Vc, e, f, X, XI, XIII, XVII, XX, and XXII were recrystallized from a mixture of hexane–ether; compounds Vd, VI, XIX, XXV, and XXVI from hexane–chloroform; and Va, b, g, h from ether–chloroform. According to [1], mp 83-84°C (Va), 125-126°C (Vb).

**Elemental analysis was not performed due to the instability of the compound.

TABLE 4. Reaction Conditions and Yields of Substituted Indolizines

Compound	Starting materials	Method	Reaction time, h	Yield, %	Eluent component ratio for chromatography*1
Va	Ia+III	B*2	2	28	2:1
Vb	Ib+III	B*2	4,5	47	2:1
Vc	Ic+III	A*3	7	90	2:1
Vd	Id+III	A	5,5	51	5:1
Ve,g	Ie+III	A*3	2	44	4:1
Vf,h	If+III	A*3	4,5	68*4	2:1
X	IX+III	A	4,5	28	4:1
XIII	XII+III	A	27	2	8:1:1
XIX, XX	Ib+XVIII	B	20	16	3:1
XXII	Ib+XXI	B	20	9	10:1
XXV, XXVI	Ib+XX	A	7,5	3	4:1

*1 For compounds Va-h, X, and XXII the eluent consisted of a hexane–ether mixture, for XIII, hexane–ether–chloroform; for XIX, XX, XXV, and XXVI, hexane–ethyl acetate mixture.

*2 Oxidizing agent, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

*3 Manganese dioxide oxidant.

*4 Calculated based on unreacted pyridine.

0.0674 and 0.0649 β^2, respectively, while the values for the formation of the 6-R-substituted indolizine are 0.0655 and 0.0612 β^2, respectively. Based on these data preferential formation of the 8-R-substituted indolizine isomers is probably due to enhanced stabilization of the corresponding transition state via charge transfer interaction.

The formation of only one regioisomer in the reaction of isoquinolinium dichloromethylide with dimethyl maleate can also be attributed to the same factors and is due to the larger coefficient for the $C_{(1)}$ atom in the isoquinoline fragment of the molecule on the HOMO of the ylide than for the $C_{(3)}$ atom (according to MO theory, about 2 times greater).

The yield of cycloaddition products from dichloromethylide derivatives decreases in the series isoquinoline, quinoline, 8-methylquinoline, while 2-substituted pyridines are inert in this reaction. The factor responsible for the observed reduction in activity of ylides containing a substituent in the ortho- or peri-position is probably the nonplanar conformation of these molecules, which inhibits or impeded their participation in cycloaddition reactions.

EXPERIMENTAL

TLC analysis of the course of reactions was carried out using Silufol UV-254 plates. GLC analyses of reaction mixtures were performed on an LKhM-80MD chromatograph equipped with a 1800 × 3 mm glass column filled with 3% SE-30 as the stationary phase on N-Super chromatone. IR spectra were recorded on a UR-20 spectrophotometer, PMR spectra on a BS-567A spectrometer (100 MHz) vs. HMDS as internal standard; the spectrum of compound VII was obtained on a Bruker WM-400 (400 MHz) instrument vs. TMS as internal standard. The pyridine and dipolarophile starting materials were all distilled samples of chemically pure grade reagents; 4-chloropyridine was prepared according to [13]. The chloroform used in these reactions had been purified to remove ethanol. The analytical characteristics of all new compounds agreed with calculations; their mp are given in Table 3.

Reaction of Pyridines Ia-f, Isoquinoline IX, and Quinoline XII with Dichlorocarbene in the Presence of Dipolarophiles. A. A mixture of 6 mmoles substituted pyridine, 9 mmoles dipolarophile, 0.48 g (12 mmoles) powdered NaOH, and 0.68 g (3 mmoles) benzyltriethylammonium chloride in 40 ml chloroform was stirred under an argon atmosphere at ca. 20°C (for reaction time, see Table 4). The reaction mixture was then filtered and the filtrate stirred with 3-5 g activated manganese dioxide [14] for about 1 h. In several cases (see Table 4), a benzene solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was used instead of manganese dioxide. The reaction mixture was again filtered and the filtrate evaporated; the products were isolated by column chromatography (100-160 μm silica gel, eluent cf. Table 4).

B. To a solution of 6 mmoles substituted pyridine, 9 mmoles dipolarophile, and 0.68 g (3 mmoles) benzyltriethylammonium chloride in an argon atmosphere at 58-60°C was added portionwise 2 g (12 mmoles) sodium trichloroacetate with stirring. Further workup of the reaction mixture was the same as in method A above.

3-Phenyl-8,8-dichloro-3a,t-5a,6,7,8,9a-hexahydroindolizino[6,5-d]isoxazole-r-6,c-7-dicarboxylic Acid Dimethyl Ester (VI). A mixture of 1.1 g (12 mmoles) 4-picoline, 1.73 g (12 mmoles) dimethyl maleate, 1.37 g (6 mmoles) benzyltriethylammonium chloride, and 0.72 g (18 mmoles) powdered NaOH in 40 ml chloroform was stirred under argon at ca. 20°C for 4 h. The reaction mixture was filtered and the filtrate mixed with 1.9 g (12 mmoles) benzohydroxamic acid chloroanhydride [15], while 1.2 g (12 mmoles) triethylamine was added and the mixture stirred 5 h. The reaction mixture was then evaporated and the residue subjected to column chromatography (100-160 μm silica gel, hexane–ether 4:1 eluent) to give 0.15 g (28%) compound VI, along with indolizine Vb and the reaction product of 4-picoline with benzonitrile oxide. Upon standing in solution compound VI was converted to the dimethyl ester of 8-oxo-3-phenyl-3a,t-5a,6,7,8,9a-hexahydroindolizino[6,5-d]isoxazole-r-6,c-7-dicarboxylic acid (VII).

Pyrrolo[1,2-a]isoquinoline-1,2-dicarboxylic Acid Dimethyl Ester (XI). A solution of 1 mmole compound X in benzene was treated with a benzene solution containing an equimolar amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and the resulting mixture was filtered and the filtrate evaporated; TLC workup (Silpearl silica gel, hexane–ether 2:1 eluent) gave 0.8 mmoles compound XI.

7-Methylindolizine-1,2-dicarboxylic Acid Dimethyl Ester (XVII). The reaction of 4-picoline and dimethyl fumarate was carried out using Method A for 4 h. The reaction mixture was filtered and 0.6 g (6 mmoles) triethylamine was added; after 2.5 h the reaction mixture was evaporated and column chromatography workup (silica gel 100-160 μm, hexane–ether 3:1 eluent) gave 0.38 g (26%) compound XVII.

LITERATURE CITED

1. A. F. Khlebnikov and R. R. Kostikov, Khim. Geterotsikl. Soedin., No. 6, 856 (1987).
2. O. Tsuge, S. Kanemasa, and S. Takenaka, Bull. Chem. Soc. Jpn., 59, 3631 (1986).
3. G. A. Henrick, E. Ritchie, and W. C. Taylor, Aust. J. Chem., 20, 2467 (1967).
4. M. T. Gandasegui and J. Alvarez-Builla, J. Chem. Res. (S), No. 2, 74 (1986).
5. R. A. Abramovitch and V. Alexanian, J. Org. Chem., 41, 2144 (1976).
6. P. H. Wadsworth, N. L. Bender, D. L. Smith, and H. R. Luss, J. Org. Chem., 51, 4639 (1986).
7. Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, Tetrahedron, 28, 21 (1972).
8. M. J. S. Dewar and W. Thiel, J. Am. Chem. Soc., 99, 4899 (1977).
9. G. Suprateanu and A. Lablache-Combier, Heterocycles, 22, 2079 (1984).

10. K. N. Houk and K. Yamaguchi, 1,3-Dipolar Cycloaddition Chemistry (A. Padwa, ed.), Wiley, New York (1984), Vol. 1, p. 407.
11. T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, J. Org. Chem., 36, 813 (1971).
12. M. Dewar and R. Doherty, Perturbation Molecular Orbital Theory in Organic Chemistry [Russian translation], Mir, Moscow (1977), p. 96.
13. Yu. I. Chumakov, Pyridine Bases, Tekhnika, Kiev (1965), p. 99.
14. I. Attenborrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, J. Chem. Soc., No. 3, 1094 (1952).
15. A. Q. Hussein, M. M. El-Abadelah, and W. C. Sabr, J. Heterocycl. Chem., 20, 301 (1983).

STEREOCHEMISTRY OF THE REACTION OF PYRIDINIUM YLIDES WITH α,β-UNSATURATED NITRILES

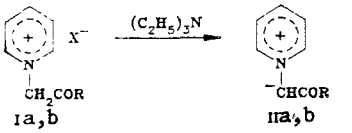
A. M. Shestopalov, Yu. A. Sharanin, and V. P. Litvinov

UDC 547.821.3:543.422:541.634

Regioselective and stereoselective methods were developed for the synthesis of 4-aryl-2-oxo-3-(1-pyridinio)-5-cyano-3,4-trans-1,2,3,4-tetrahydropyridin-6-olates from pyridinium ylides and α,β-unsaturated nitriles. The compounds were also obtained by the condensation of aromatic aldehydes, cyanoacetamide, and pyridinium ylides. It was established that these reactions take place through the corresponding Michael adducts, which undergo heterocyclization in the form of the anti conformers to substituted 3,4-trans-1,2,3,4-tetrahydropyridin-6-olates.

The high reactivity of pyridinium ylides is due to the electron-withdrawing action of the pyridinium cation. Thus, pyridinium ylides enter readily into nucleophilic Michael addition to unsaturated compounds [1-3]. Here various heterocyclic nitrogen compounds are formed, depending on the conditions and on the structure of the initial compounds, i.e., pyridines, quinolines, indolizines, imidazopyridines, and others [1-5]. Pyridinium ylides have found wide use in the synthesis of pyridines, bipyridyls, and polypyridyls [2, 3, 6-8]. α,β-Unsaturated ketones and aldehydes of the aliphatic, carbocyclic, and heterocyclic series were investigated as unsaturated compounds.

Unsaturated nitriles containing an activated C=C double bond also enter readily into nucleophilic addition [9-11]. Until now, however, their reactions have hardly been investigated at all except for the reaction of acrylonitrile [12] with pyridinium ylides. In view of this we studied the reaction of the arylidene derivatives of cyanoacetic ester and cyanoacetamide with pyridinium ylides. Here the pyridinium ylides were not isolated in the individual state but were generated in the reaction mixture from the corresponding pyridinium salts by the action of bases



Ia,b IIa,b

I, IIa X=Cl, R=NH_2; b X=Br, R=OC_2H_5

We found that when the pyridinium ylides are generated from the pyridinium salts (Ia, b) in boiling acetic acid in the presence of ammonium acetate by analogy with the method in

T. G. Shevchenko State Pedagogical Institute, Lugansk 348011. N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 363-369, March, 1990. Original article submitted July 25, 1988; revision submitted January 18, 1989.