STRUCTURES AND AMBIPHILIC REACTIVITIES OF INDOLIZINES.

5.* ACYLATION OF 2-METHYLINDOLIZINE

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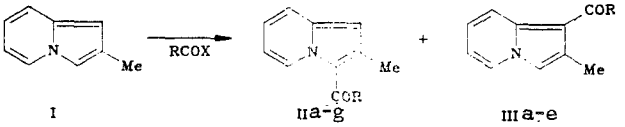
UDC 547.759.4:542.951:543.51'422.25

The acylation and carbomethoxylation of 2-methylindolizine were studied. In most cases minor amounts of the 1-substituted isomers were isolated in addition to the "usual" products of substitution in the 3 position. The data from the PMR and mass spectra of the 2-methyl-3- and 1-acylindolizines obtained are discussed.

It is generally accepted that indolizines undergo electrophilic substitution in the 3 position [2]. According to the result of quantum-chemical calculations (for example, see [3-5]), the 3 position is more preferable for the occurrence of S_E reactions than the 1 position, but the difference in reactivities should be small. Trace amounts of 1-substituted indolizines were isolated in addition to the "usual" products of substitution in the 3 position in the formylation (by the Vilsmeier reaction) and nitrosation of indolizine [6]. It might be assumed that the minor 1-substituted indolizines are also formed (but were not noted) in other electrophilic substitution reactions in the indolizine series.

In the present research, within the framework of our investigation of the reactivities of indolizines, we studied the electrophilic acylation of 2-methylindolizine (I) by the action of acetic and trifluoroacetic anhydrides and benzoyl, trimethylacetyl, and di- and trichloroacetyl chlorides, as well as carbomethoxylation by the action of ClCOOMe. Principal attention was directed to the thorough chromatographic monitoring of the reaction products and the isolation of the minor components. The acetylation [7], benzoylation [8], and carbethoxylation [9] of 2-methylindolizine with the isolation of 3-substituted compounds as the only products have been previously carried out. The di- and trihaloacetylation of indolizines have not been studied.

It was found that acylation (and carbomethoxylation) leads in most cases to the formation of, in addition to the expected 3-substituted IIa-g, very small amounts (1-6%) of the 1-substituted isomers IIIa-e. Thus the indolizine ring displays ambident character in the investigated S_E reactions. Let us note that indolizines IIIa, c, d were previously obtained by cyclization of N-substituted pyridinium salts [10-12]. In the trifluoroacetylation reaction, in addition to isomers IIe and IIIe, we isolated 2-methyl-3H-indolizinium trifluoroacetate (IV), which is formed from the starting indolizine I and the liberated CF_3COOH; carrying out the reaction in the presence of sodium carbonate, which ties up the acid, made it possible to increase the yield of IIe somewhat. The formation of 1-substituted isomers was not observed in the di- and trichloroacetylation reactions. The characteristics of the compounds obtained are presented in Table 1, while data from the PMR and mass spectra are presented in Tables 2 and 3.



I IIa-g IIIa-e

II, III a R=Me; b R=*t*-Bu; c R=Ph; d R=MeO; e R=CF_3; f R=CCl_3; g R=$CHCl_2$

The νCO vibrational frequencies are usually lower and the color is usually deeper for 3-acylindolizines than for the 1-substituted isomers – evidently as a consequence of the greater conjugation in the 3-substituted compounds. The differences in the IR and UV spectra,

*See [1] for Communication 4.

M. V. Lomonosov Moscow State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1634-1638, December, 1989. Original article submitted April 13, 1988.

 0009-3122/89/2512-1360$12.50

TABLE 1. Characteristics of 2-Methyl-3- and 1-Acyl-Indolizines

Reagent	Indolizine: R in RCO	Indolizine: substituent position	Indolizine: No.	R_f*	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max} (log ε) (in ethanol)	Yield, %
Ac_2O; Et_3N	Me	3	IIa	0,46	1610	369 (3,91)	87
		1	IIIa	0,30	1610, 1635	362 (3,56)	1,5
t-BuCOCl	*t*-Bu	3	IIb	0,95	1705	373 (3,64)	55
		1	IIIc	0,60	1695	360 (3,39)	1
PhCOCl; Et_3N	Ph	3	IIc	0,50	1600	382 (4,13)	84
		1	IIIc	0,40	1605	394 (3,89)	6
ClCOOMe	MeO	3	IId	0,75	1680	341 (4,13)	86
		1	IIId	0,45	1695	336 (2,62)	1
$(CF_3CO)_2O$	CF_3	3	IIe	0,65	1610, 1630	382+390 (4,00; 4,01)	93
		1	IIIe	0,35	1620, 1640	366 (4,20)	3,5
CCl_3COOH+ $POCl_3$	CCl_3	3	IIf	0,75	1635	388 (3,89)	85
$CHCl_2COOH$+ $POCl_3$	$CHCl_2$	3	IIg	0,56	1615	393 (4,17)	90

*Hexane–ethyl acetate (5:1).

TABLE 2. Data from the PMR Spectra of 3(1)-Aceylindolizines

Indolizine	1(3)-H	2-Me	5-H	6-H	7-H	8-H	Substituent
IIb*	6,07	2,50	8,77	6,40	6,70	7,30	1,3
IIc*	6,35	1,95	9,81	6,86	7,15	***	7,40 ... 7,65
IIIc**	***	2,10	8,16	6,80	7,05	8,16	7,4 ... 7,7
IId**	6,30	2,56	9,43	6,71	6,96	7,35	3,93
IIId [12]	6,88	2,40	7,74	6,46	6,72	8,05	3,79
IIe**	6,10	2,35	9,70	6,71	7,0 ... 7,3		—
IIIe*	7,03	2,43	7,93	6,75	7,17	8,25	—
IIf*	6,26	2,70	9,60	6,72	7,03	7,3	—
IIg**	6,45	2,75	10,07	7,00	7,31	7,51	6,87

*In CCl_4.
**In $CHCl_3$.
***Falls in the region of absorption of the substituent.

however, are slight and cannot be used to assign the isomers. The PMR spectra are substantially more informative in this sense. Thus, in the case of the 3-substituted isomers the resonance signal of the 5-H proton undergoes a significant (>1.0 ppm) weak-field shift, which is due to the magnetically anisotropic acyl (methoxycarbonyl) group in the peri position. In the case of the 1-substituted isomers the signal of the 8-H proton undergoes a similar weak-field shift under the influence of the peri-oriented 1-COR group. As a result, the weak-field part of the PMR spectrra of 3(1)-substituted indolizines II and III proves to be diagnostic for the assignment of the isomers. Let us note that the literature PMR spectra of indolizines IIa and IIIa [10], 2-methyl-3- and 1-ethoxycarbonylindolizines [9, 13], 3- and 1-formylindolizines [6], and 3- and 1-thioformyl-2-tert-butylindolizines [14] are subject to the principles indicated above.

In the present research we also studied the mass spectra of the indolizines IIa-g and IIIa-e obtained.* For all of the compounds there is a common fragmentation pathway that includes the elimination from the molecular ion M^+ of the radical R of the acyl group with the formation of ions at 158;† the subsequent splitting out of a molecule of CO leads to the ion at 130, to which one can assign a quainolizinium cation structure [15]. In the case of indolizine IIIc the principal fragmentation pathway is the splitting out from M^+ of a methylindolizine radical with the formation of a $PhCO^+$ ion (105), the peak of which is the most intense in the mass spectrum. On the basis of Stevenson's rule it may be concluded that the energy of ionization of the benzoyl radical is lower than the energy of ionization of the methyl-indolizine radical.

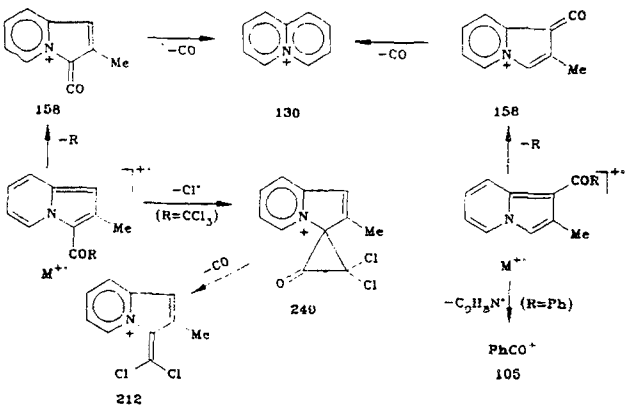
Intense peaks of $[M - H]^+$ ions are observed in the mass spectra of indolizines IIc and IIIc. Peaks of $[M - OH]^+$ (218), $[M - H_2O]^+$ (217), $[M - CO]^+$ (207), and $[M - HCO]^+$ (206) ions are also observed in the spectrum of IIc. In the case of trichloroacetylindoli-

*The authors thank O. A. Solov'ev for recording the mass spectra and P. B. Terent'ev for his useful discussion.
†In the text and in the scheme the numbers that characterize the ions are the m/z values.

TABLE 3. Data from the Mass Spectra of 2-Methyl-3(1)-acylindolizines*

Compound	m/z (peak intensity, %)	W_M	$S_{1/2}$
IIa	174 (8), 173 (63), 159 (12), 158 (100), 131 (11), 130 (58), 128 (10), 105 (11), 103 (27), 102 (8), 78 (16), 77 (33), 51 (25)	17,8	3
IIIa	174 (7), 173 (52), 159 (16), 158 (100), 131 (8), 130 (34), 128 (7), 105 (17), 104 (8), 103 (32), 102 (9), 78 (14), 77 (31), 51 (39)	15,8	3
IIb	215 (10), 189 (8), 159 (12), 158 (100), 149 (12), 131 (19), 130 (39), 105 (41), 103 (27), 83 (26), 77 (40), 69 (28), 57 (32), 55 (49), 51 (25)	2,2	4
IIIb	215 (15), 159 (18), 158 (100), 131 (12), 130 (27), 128 (10), 105 (27), 103 (22), 77 (39), 51 (26)	5,1	3
IIc	236 (8), 235 (88), 234 (100), 220 (11), 218 (10), 217 (9), 207 (7), 206 (15), 205 (6), 204 (11), 191 (6), 158 (39), 130 (55), 105 (25), 103 (37), 78 (36), 77 (65), 51 (42)	13,1	5
IIIc	235 (5), 234 (4), 205 (4), 177 (8), 162 (5), 158 (10), 149 (6), 135 (11), 134 (13), 130 (6), 123 (5), 122 (6), 106 (9), 105 (100), 78 (9), 77 (90), 57 (21), 55 (21)	1,5	2
IId	190 (12), 189 (100), 159 (11), 158 (69), 140 (20), 131 (8), 130 (80), 105 (77), 103 (33), 102 (23), 78 (23), 77 (77), 63 (23), 51 (45)	18,7	4
IIId	189 (27), 158 (25), 140 (32), 130 (23), 125 (16), 106 (23), 105 (100), 103 (34), 79 (23), 78 (23), 77 (50), 51 (50)	6,3	4
IIe	228 (6), 227 (39), 159 (17), 158 (100), 131 (11), 130 (55), 129 (8),128 (9), 105 (18), 104 (9), 103 (35), 102 (10), 79 (11), 78 (12), 77 (45), 65 (16), 51 (39)	10,0	4
IIIe	228 (6), 227 (42), 159 (16), 158 (100), 131 (6), 130 (40), 129 (8), 128 (10), 104 (9), 103 (33), 102 (13), 79 (12), 78,5 (7), 78 (12), 77 (38), 76 (7), 75 (10), 65 (12), 51 (39)	11,4	4
IIf	279 (2), 277 (7), 275 (5), 240 (3), 214 (10), 212 (12), 159 (15), 158 (100), 142 (6), 141 (6), 130 (38), 128 (7), 103 (15), 102 (7), 78 (11), 77 (25), 51 (14)	4,7	3
IIg	243 (9), 241 (13), 214 (5), 212 (4), 185 (18), 183 (19), 178 (18), 159 (14), 158 (100), 157 (9), 155 (9), 144 (5), 143 (7), 142 (10), 141 (7), 131 (6), 130 (42), 128 (6), 103 (19), 102 (11), 78 (17), 77 (25), 76 (21), 75 (17), 51 (26)	5,0	6

*The peaks of ions with intensities no less than 5% of the maximum peak are presented; the intensities are given in parentheses.



zine IIf, in addition to splitting out of a CCl_3 radical, one observes the elimination of a chlorine atom from the molecular ion and then, after the formation of a spiro cation with m/z 240, a molecule of OC (see the scheme). Thus, the mass spectra can, in principle, be used for the identification of isomeric 3- and 1-benzoylindolizines.

EXPERIMENTAL

The IR spectra of suspensions or films of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were obtained with a Cary-219 spectrophotometer. The PMR spectra of solutions in $CDCl_3$ and CCl_4 were recorded with a Tesla BS-467 spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with an MKh-1303 spectrometer by the method of direct introduction of the samples at an ionization energy of 70 eV. The purification and separation of the substances were carried out chromatographically with columns and plates; L 40/100 silica gel and Silpearl were used as the sorbents. Characteristic colors of chromatographic spots – blue in the case

of the 1-substituted isomers – appeared in the development of the chromatographic plates with Ehrlich's reagent after heating. Hexane was used for recrystallization of acylindolizines IIa, c-g and IIa, e (see below). 2-Methylindolizine was synthesized by the method described in [16]. Results of elementary analysis of IIb, d-g were in agreement with calculated values.

Trifluoroacetylation of 2-Methylindolizine. A mixture of 0.765 g (5.8 mmole) of indolizine I and 1.34 g (6.4 mmole) of trifluoroacetic anhydride in 20 ml of benzene was maintained at room temperature for 5 min. After evaporation, the reaction mixture was chromatographed with a column [heptane–ethyl acetate (4:1)]. Workup of the first fraction (R_f 0.70) gave 1.12 g (84%) of light-yellow crystals of 2-methyl-3-trifluoroacetylindolizine (IIe) with mp 64°C. Workup of the second fraction (R_f 0.40) gave 40 mg (3%) of yellowish crystals of 2-methyl-1-trifluoroacetylindolizine (IIIe) with mp 78°C. Subsequent elution with ether made it possible to isolate salt IV; its PMR spectrum was identical to the previously described spectrum [17]. Carrying out the reaction in the presence of sodium carbonate made it possible to raise the yield of IIe to 93% (IIIe was also isolated in 3.5% yield); salt IV was not formed in this case.

Acetylation of 2-Methylindolysine. A mixture of 1.46 g (11.1 mmoles) indolysine I, 5 ml (53 mmoles) acetic anhydride, and 1 ml (7 mmoles) triethylamine was boiled for 30 min. The reaction mixture was evaporated, and the residue chromatographed on a column (hexane–ethyl acetate, 5:1). Yield 1.86 g (87%) 2-methyl-3-acetylindolysine (IIa), mp 83...84°C (according to the data of [7, 10], mp 83°C) and 27 mg (1.5%) 2-methyl-1-acetylindolysine (IIIa), mp 70°C (according to the data of [10], mp 69...71°C).

A similar method involving the reaction of 1.07 g (8.2 mmole) of indolizine I, 1.5 ml (12.8 mmole) of benzoyl chloride, and 1 ml (7 mmole) of triethylamine gave 1.58 g (84%) of 2-methyl-3-bezoylindolizine (IIc), with mp 65°C (mp 63°C [8]), and 0.12 g (6%) of 2-methyl-1-benzoylindolizne (IIIc) in the form of a yellow oil.

Carbomethoxylation of 2-Methylindolizine. A mixture of 1.08 g (8.2 mmole) of indolizine I and 5 ml (65 mmole) of ClCOOMe was refluxed for 2 h, after which 3 ml (40 mmole) of ClCOOMe was added, and the mixture was refluxed for another 2 h. Evaporation of the reaction mixture and chromatogrpahy [hexane–ethylacetate (5:1)] gave 1.25 g (86%) of 2-methyl-3-methoxycarbonylindolizine (IId) in the form of a colorless oil and 18 mg (1%) of 2-methyl-1-methoxycarbonylindolizine (IIId) in the form of a colorless oil that could not be crystallized (mp 40-41°C [12]).

A similar method involving the reaction of 0.70 g (5.3 mmole) of indolizine I and 3 ml (16.6 mmole) of pivaloyl chloride (refluxing for 10 h in 10 ml of benzene with the addition of sodium carbonate in portions) gave 0.63 g (55%) of 2-methyl-3-pivaloylindolizine (IIb) in the form of a yellowish liquid and 20 ml (1%) of 2-methyl-1-pivaloylindolizine (IIIb) in the form of a yellow oil.

2-Methyl-3-dichloroacetylindolizine (IIg). A mixture of 0.22 g (1.7 mmole) of indolizine I, 0.3 ml [0.47 g (3.6 mmole)] of dichloroacetic acid, and 2 ml [3.4 g (22 mmole)] of $POCl_3$ in 10 ml of chloroform was refluxed for 4 h with the addition of sodium carbonate in portions, after which the mixture was poured into 10 ml of water, and the organic layer was dried over Na_2SO_4 and evaporated. chromatography on a plate gave 0.365 g (90%) of 2-methyl-3-dichloroacetylindolizine (IIg) in the form of bright-yellow crystals with mp 147°C.

A similar method involving the reaction of 0.19 g (1.45 mmole) of indolizine I, 1.0 g (6 mmole) of trichloroacetic acid, and 5 ml of $POCl_3$ gave, after chromatography on a plate [hexane–ethyl acetate (5:1)], 0.34 g (85%) of 2-methyl-3-trichloroacetylindolizine (IIf) in the form of bright-yellow crystals with mp 62°C.

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SYNTHESIS AND PROPERTIES OF THIOCARBAMOYLMETHYLPYRIDINIUM (ISOQUINOLINIUM) YLIDS

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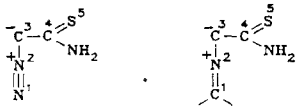
UDC 547.821.3'833.1'298.4'239.2.07:543.422

2-(2-Carbethoxy-1-amino-1-thio)ethylenepyradinium(isoqunolinium) ylids were obtained by the reaction of carbethoxycyanomethylpyridinium(isoquinolinium) ylids with hydrogen sulfide. In an alkaline medium they cyclize into 5-mercaptosubstituted imidazo[1,2-a]pyridines(isoquinolines). The structure of the latter compounds was confirmed by PMR and IR spectroscopy.

Thiocarbamolyazomethine ylids are represented in the literature by scattered examples [1-4]. However, on the basis of the known data on the ability of the thio derivatives of heterocyclic azomethine ylids to undergo intramolecular cyclization [3-5], and as the result of the high chemical activity of the thioamide group, it could be expected that the thiocarbamoyl azomethine ylids will serve as convenient starting compounds in the synthesis of condensed heterocycles.

The present article deals with the synthesis and investigation of thiocarbamoylmethylpyridinium(isoquinolinium) ylids and their heterocyclization into imidazole and thiazole derivatives, which are of interest as biologically active compounds [6, 7].

To develop methods of synthesis of thioamides I, we studied the sulfhydrylation of the corresponding nitriles II. We found that the cyano group in compounds II has low reactivity with respect to hydrogen sulfide and only partially converts into the thioamide group when the reaction is carried out at elevated temperature and pressure in the presence of sodium ethylate. Thioamides Ia, b were isolated in yields of from 10 to 40%, while the variation of the catalysts, solvents and the use of a large excess of hydrogen sulfide did not lead to an increase in the degree of conversion of nitrile into thioamide.



In contrast to aliphatic α-diazothioamides, which cyclize into 1,2,3-thiadiazoles even under the conditions of their formation [8], the expected cyclization of thioamides I, which are analogs of α-diazothioamides with isoionic substitution at the 1-position, into thiazoles III did not take place either at elevated temperatures or at various pH values of the medium.

Thioamidates IV were not obtained, from methylaton of thioamides Ia, b by methyl iodide in an ethanolic solution of sodium ethylate, but instead 2-methylthio-3-carbethoxyimidazo[1,2-a]-pyridine (Va) and 2-methylthio-3-arbethoxyimidazo[1,2-a]isoquinoline (Vb) were formed, which, according to the IR and UV spectral data, were identical to the compounds obtained previously by another method [9]. These compounds are probably formed as the result of two

S. M. Kirov Ural' Polytechnical Institute, Sverdlovsk 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1639-1643, December, 1989. Original article submitted May 6, 1988.

 0009-3122/89/2512-1364$12.50