SYNTHESIS AND PROPERTIES OF 1-METHYL(ARYL)-7-ETHOXYCARBONYLINDOLIZINES

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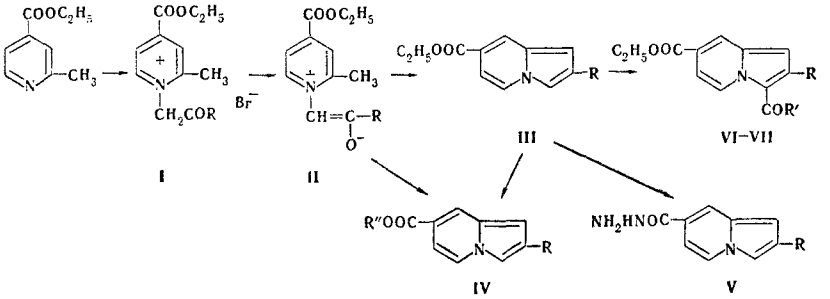
The previously unknown 2-substituted indolizine-7-carboxylic acids and their derivatives were synthesized, and some of their properties were studied.

A communication regarding the synthesis of 2-methyl-8-ethoxycarbonylindolizine appeared in 1972 [1], but the properties and transformations of this compound have not been studied.

From the point of view of the mutual effect of the pyrrole and pyridine rings in the condensed systems on the reactivities of the compounds obtained it seemed of interest to us to synthesize the previously unknown esters of 2-substituted indolizine-7-carboxylic acids and investigate some of their nucleophilic and electrophilic substitution reactions.

Indolizines III were obtained via the following scheme:



I, II, III, V a R=CH_3; b R=C_6H_5; IV a R=C_6H_5, R″=Na; b R=C_6H_5, R″=H; VI a R=R′=CH_3; b R=CH_3, R′=C_6H_5; c R=CH_3, R′=C_6H_4Cl-*p*; VII a R=C_6H_5, R′=CH_3; b R=R′=C_6H_5; c R=C_6H_5, R′=C_6H_4Cl-*p*

Ethyl 2-methylisonicotinate was converted to quaternary pyridinium salts I by reaction with bromoacetone and phenacyl bromide. Cyclization of salts I by the standard Chichibabin method by heating with aqueous sodium bicarbonate solution gave a negative result for salt Ia (the reaction proceeded with pronounced resinification), while sodium 2-phenylindolizine-7-carboxylate was obtained in 60.7% yield from salt Ib under these conditions. As a consequence of the extremely low solubility of the sodium salt in water and organic solvents, further transformations of it proved to be difficult, and this restricted the practical possibilities of this synthetic method. Other methods for the conversion of quaternary salts Ia and Ib to indolizines were studied. The most efficient method for the synthesis of ethyl 2-phenylindolizine-7-carboxylate (IIIb) was conversion of salt Ib to anhydro base IIb by the action of ammonium hydroxide or aqueous sodium carbonate solution and subsequent cyclization of IIb by heating in an organic solvent. However, we were unable to synthesize indolizine IIIa by means of this method. As in the first case, the formation of a bright-colored anhydro base, which, in the case of IIa, was not isolated because of its high solubility in water, was

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TABLE 1. Chemical Shifts of the Protons of 2-Methyl(phenyl)-3-acyl-7-ethoxycarbonylindolizines

Compound	H_1	H_5	H_6	H_8	CH_2	CH_3	R_1	R_2
VIa	6,50	9,86	7,28	8,08	4,39	1,40	2,59	2,56
VIb	6,53	9,53	7,31	8,15	4,40	1,40	1,95	7,00—7,70
VIc	6,53	9,55	7,28	8,16	4,39	1,42	1,98	7,35—7,70
VIIa	6,66	9,88	7,33	8,20	4,40	1,41	~7,40	2,08
VIIb	6,81	9,53	~7,30	8,28	4,42	1,43	~7,00	6,80—7,50
VIIc	6,81	9,54	~7,35	8,28	4,42	1,42	~7,05	6,90—7,50

observed during the action of ammonium hydroxide or an equivalent amount of sodium hydroxide on salt Ia. A small amount of 2-methylindolizine-7-carboxamide was formed on subsequent heating of the ammonia solution. Ethyl 2-methylindolizine-7-carboxylate (IIIa) was obtained by heating quaternary salt Ia in absolute ethanol in the presence of sodium bicarbonate.

The hydrazination of esters IIIa and IIIb was studied. Reaction with hydrazine hydrate proceeded only on prolonged refluxing of IIIa and IIIb with a slight excess of hydrazine hydrate. The considerably more severe conditions necessary for the preparation of hydrazides of 2-substituted indolizine-7-carboxylic acids from their esters as compared with the conditions for the conversion of the esters of isonicotinic acid to its hydrazide attest to the substantial effect of the π-electron system of indolizine [2] on the carbethoxy group, which leads to an increase in the electron density on the carbonyl carbon.

The acylation of indolizines III – an electrophilic substitution reaction – proceeds quite completely under mild conditions to give 3-acylindolizines. The position of the acyl residues was unambiguously established from PMR spectral data.

The chemical shifts of the protons of VIa-c and VIIa-c are presented in Table 1. The signals were assigned to the protons of the indolizine ring on the basis of a comparison of the observed spin–spin coupling constants ($J_{H_1H_5} \approx 0.8$ Hz, $J_{H_1H_6}$, $J_{H_1H_8} \leq 0.4$ Hz, $J_{H_5H_6} \approx 7.5$ Hz, $J_{H_5H_8} \approx 1$ Hz, and $J_{H_6H_8} \approx 1.9$ Hz) with the corresponding literature data [3].

Analysis of the data in Table 1 shows that the signal of the H_5 proton in all of the investigated compounds is observed at very weak field (9.5 ~ 9.9 ppm) as compared with unsubstituted indolizine (7.76 ppm [3]). A number of investigators have noted that ester, aldehyde, thioaldehyde, and acyl substituents in the 3 position strongly deshield the protons attached to C_5 of the indolizine ring [1, 4, 5]. The indicated weak-field shift of the H_5 signal in the spectra of VIa-c and VIIa-c therefore unambiguously attests to the presence of an acyl substituent in the 3 position in these compounds.

EXPERIMENTAL

The PMR spectra of deuterochloroform solutions of the compounds were recorded with a JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard (δ 0.04 ppm).

1-Acetonyl-2-methyl-4-ethoxycarbonylpyridinium Bromide (Ia). A solution of 10 g (60 mmole) of ethyl 2-methylisonicotinate and 8.3 g (60 mmole) of bromoacetone in 25 ml of acetone was refluxed for 12 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with acetone to give 16.8 g (91.5%) of a product with mp 105-107° (from acetone). Found: C 47.2; H 5.4; Br 26.0%. $C_{12}H_{16}BrNO_3$. Calculated: C 47.6; H 5.4; Br 26.3%.

A similar procedure was used to prepare 1-acetonyl-2-methyl-4-methoxycarbonylpyridinium bromide, with mp 107-109° (from acetone–ethanol), in 52.5% yield from methyl 2-methylisonicotinate and bromoacetone. Found: C 45.5; H 5.0; Br 27.7%. $C_{11}H_{14}BrNO_3$. Calculated: C 45.8; H 4.9; Br 27.8%.

1-Phenacyl-2-methyl-4-ethoxycarbonylpyridinium Bromide (Ib). This compound, with mp 138-139° (from acetone), was obtained in 78% yield by the method used to prepare Ia. Found: Br 22.0%. $C_{17}H_{18}BrNO_3$. Calculated: Br 21.9%.

1-Phenacyl-2-methyl-4-ethoxycarbonylpyridinium Anhydro Base (IIb). A 15-ml sample of a 25% ammonium hydroxide solution was added to a solution of 10 g (27.4 mmole) of Ib in 75 ml of water. A copious orange precipitate of the anhydro base formed. The mixture was cooled for 1 h at 0 deg, and the precipitate was removed by suction filtration, washed with water, and dried to give 7.4 g (95%) of IIb. Found: C 71.9; H 6.0%. $C_{17}H_{17}NO_3$. Calculated: C 72.1; H 6.0%.

2-Methylindolizine-7-carboxamide. A solution of 5 g (33 mmole) of methyl 2-methylisonicotinate and 4.5 g (33 mmole) of bromoacetone in 30 ml of acetone was refluxed for 12 h, after which the mixture was vacuum evaporated, and the residue was dissolved in 50 ml of water. The aqueous solution was extracted with ether and treated with 15 ml of 25% ammonium hydroxide. Cooling of the solution precipitated the bright-red anhydro base (0.2 g), which was removed by filtration and washed with a small amount of cold water. The substance decomposed on standing in air and also in a vacuum desiccator. The aqueous ammonia solution was heated for 3 h on a water bath, and the precipitated crystals were removed by filtration and recrystallized from ethanol to give a product with mp 209-210°. Found: C 69.2; H 5.8; N 16.0%. $C_{10}H_{10}N_2O$. Calculated: C 69.3; H 5.8; N 16.1%.

Ethyl 2-methylindolizine-7-carboxylate (IIIa). A mixture of 9.2 g (30 mmole) of Ia, 5.1 g (60 mmole) of sodium bicarbonate, and 120 ml of absolute ethanol was refluxed with vigorous stirring for 3 h. The ethanol was then removed by vacuum distillation, and the residue was dissolved in 60 ml of water. The aqueous solution was extracted with ether to give 3 g (49%) of a product with mp 55-57° (from hexane). Found: C 70.6; H 6.3; N 7.0%. $C_{12}H_{13}NO_2$. Calculated: C 70.6; H 6.4; N 6.9%. Methyl 2-methylindolizine-7-carboxylate, with mp 74-76° (from hexane), was similarly obtained in 28% yield from 1-acetonyl-2-methyl-4-methoxycarbonylpyridinium bromide. Found: C 69.6; H 5.9; N 7.4%. $C_{11}H_{11}NO_2$. Calculated: C 69.9; H 5.9; N 7.4%.

Ethyl 2-Phenylindolizine-7-carboxylate (IIIb). A) A 7.4-g (26 mmole) sample of IIa was dissolved by heating in 70 ml of 2-propanol, and the solution was refluxed for 10 min. It was then cooled at 4° for 24 h, and the precipitated colorless crystals were removed by suction filtration and washed with 2-propanol to give 5.8 g (83.5%) of a product with mp 142-143° (from acetone). Found: C 77.0; H 5.9%. $C_{17}H_{15}NO_2$. Calculated: C 77.0; H 5.7%.

B) A 7.4-g (70 mmole) sample of sodium bicarbonate was added to a solution of 12 g (33 mmole) of IIa in 70 ml of water. A bright-orange precipitate of the anhydro base formed. The reaction mass was heated on a boiling-water bath for 4 h, during which the color of the precipitate changed from orange to greenish. The mixture was cooled, and the precipitate was removed by filtration and washed with water to give 5.2 g (60.7%) of sodium 2-phenylindolizine-7-carboxylate (IVa), which was practically insoluble in cold and hot water. The product did not melt on heating to 350°.

2-Phenylindolizine-7-carboxylic Acid (IVb). A) A suspension of 0.5 g (20 mmole) of sodium salt IVa in 30 ml of concentrated hydrochloric acid was refluxed for 4 h, during which the color of the precipitate changed from light-green to light-yellow, but it did not dissolve. The mixture was cooled, and the precipitate was removed by filtration and washed with water to give 0.4 g (89%) of a product with mp 274-276° (dec., from ethanol). Found: C 75.9; H 4.8; N 5.8%. $C_{15}H_{11}NO_2$. Calculated: C 75.9; H 4.7; N 5.9%.

B) A suspension of 0.5 g (19 mmole) of IIIb in 50 ml of concentrated hydrochloric acid was refluxed for 3 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with water to give 0.4 g (87%) of a product with mp 274-276° (dec.). The acids obtained by the two methods were identical according to their IR spectra. A homogeneous solution was formed by heating a suspension of acid IVb in a 20-fold amount of 10% ethanolic hydrogen chloride solution for 10 h. Cooling of this solution precipitated ester IIIb with mp 137-139° (from acetone). The esters obtained by esterification of acid IVb and cyclization of anhydro base IIb were identical.

2-Methylindolizine-7-carboxylic Acid Hydrazide (Va). A suspension of 0.5 g (2.46 mmole) of ester IIIa in 6 ml of hydrazine hydrate was refluxed for 20 h. The resulting precipitate was removed by suction filtration and washed repeatedly with water to give 0.4 g (84%) of a product with mp 158-159° (from water). Found: C 63.2; H 5.8; N 22.2%. $C_{10}H_{11}N_3O$. Calculated: C 63.5; H 5.8; N 22.2%.

2-Phenylindolizine-7-carboxylic Acid Hydrazide (Vb). This compound, with mp 224-225° (dec.), was obtained in 93% yield by the method used to prepare Va. The product was obtained as light-green crystals that were insoluble in water, acids, and ordinary organic solvents. Found: C 71.7; H 5.2; N 16.3%. $C_{15}H_{13}N_3O$. Calculated: C 71.7; H 5.2; N 16.7%.

2-Phenylindolizine-7-carboxylic acid N-acetylhydrazide, with mp 273-274° (dec.), was formed when the hydrazide was heated in glacial acetic acid until all of the solid had dissolved. Found: C 69.2; H 5.2; N 14.2%. $C_{17}H_{15}N_3O_2$. Calculated: C 69.6; H 5.1; N 14.3%.

Ethyl 2-Methyl-3-acetylindolizine-7-carboxylate. A mixture of 0.5 g (2.46 mmole) of IIIa and 5 ml of acetic anhydride was refluxed for 14 h, after which the solution was vacuum evaporated, and the residue

was recrystallized from ether–petroleum ether to give 0.4 g (67%) of a product with mp 104-106°. Found: C 68.5; H 6.1%. $C_{14}H_{15}NO_3$. Calculated: C 68.5; H 6.2%.

Ethyl 2-Phenyl-3-acetylindolizine-7-carboxylate (VIIa). A mixture of 2 g (7.5 mmole) of IIIb and 40 ml of acetic anhydride was refluxed for 30 h. The acetic anhydride was then removed by vacuum distillation, and the residue was mixed with 25% potassium carbonate solution. The carbonate solution was extracted with ether to give 2 g (85%) of a product with mp 104-106° (from hexane). Found: C 74.4; H 5.5%. $C_{19}H_{17}NO_3$. Calculated: C 74.3; H 5.6%.

Ethyl 2-Methyl-3-benzoylindolizine-7-carboxylate (VIb). A solution of 1.2 g (6 mmole) of IIIa and 0.83 g (6 mmole) of benzoyl chloride in 8 ml of benzene was held at room temperature for 48 h, and the precipitated crystals were removed by suction filtration and washed with benzene to give 1.4 g (77%) of a product with mp 147-148° (from ether–acetone). Found: C 73.8; H 5.5%. $C_{19}H_{17}NO_3$. Calculated: C 74.3; H 5.5%.

Ethyl 2-Phenyl-3-benozylindolizine-7-carboxylate (VIIb). A mixture of 2 g (7.5 mmole) of IIIb and 10 ml of benzoyl chloride was heated at 70-80° for 1 h. The reaction mixture was then poured into 150 ml of petroleum ether, and the starting material was removed by filtration. The petroleum ether and excess benzoyl chloride were removed by vacuum distillation, and the residue was recrystallized from ethanol to give 1.4 g (50%) of a product with mp 93-94°. Found: C 77.8; H 5.3%. $C_{24}H_{19}NO_3$. Calculated: C 78.0; H 5.2%.

Ethyl 2-Methyl-3-(p-chlorobenzoyl)indolizine-7-carboxylate (VIc). This compound, with mp 137-139° (from ether), was obtained in 73% yield by the method used to prepare VIb. Found: C 67.0; H 4.8; Cl 10.4%. $C_{19}H_{16}ClNO_3$. Calculated: C 66.7; H 4.7; Cl 10.4%.

2-Methyl-3-(p-chlorobenzoyl)indolizine-7-carboxylic Acid. A solution of 0.31 g (7.8 mmole) of sodium hydroxide in 10 ml of ethanol was added to a solution of 2.6 g (7.8 mmole) of VIb in 150 ml of ethanol, and the mixture was refluxed for 10 h. It was then cooled, and the resulting precipitated sodium salt was removed by suction filtration, washed with alcohol, and dissolved in 100 ml of water. The aqueous solution was acidified with acetic acid, and the precipitate was removed by suction filtration and washed with water to give 2.2 g (88%) of a product with mp 177-179°. Found: C 64.8; H 4.0; Cl 11.1%. $C_{17}H_{12}ClNO_3$. Calculated: C 65.1; H 3.9; Cl 11.3%.

Ethyl 2-Phenyl-3-(p-chlorobenzoyl)indolizine-7-carboxylate (VIIc). A mixture of 2 g (7.5 mmole) of IIIb and 8 ml of p-chlorobenzoyl chloride was heated at 80-90° for 5 h, after which it was cooled and mixed with 150 ml of petroleum ether. The resulting precipitate was removed by suction filtration and washed with petroleum ether to give 2.45 g (77.53%) of a product with mp 108-110° (from ethanol). Found: C 71.3; H 4.6; Cl 8.6%. $C_{24}H_{18}ClNO_3$. Calculated: C 71.4; H 4.5; Cl 8.8%.

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