B) A 1.5-g (0.006 mole) sample of I was dissolved by heating in a small amount of ethanol, after which 0.36 g of NaOH in 5 ml of water was added. The mixture was then refluxed for 4 h, cooled, and poured into a sixfold volume of water. The resulting yellowish precipitate was removed by filtration, and the mother liquor was acidified with hydrochloric acid to give an additional amount of product. Crystallization of the product gave 0.8 g (40%) of V.

3,3-Di(2-methyl-3-indolyl)oxindole (XVI). As in method B in the preceding experiment, 0.84 g (0.003 mole) of 3-(2-methyl-3-indolyl)dioxindole (IX) gave 0.5 g (50%) of XVI with mp 290-291° (from alcohol). Found, %: C 79.7; H 5.2; N 10.7. $C_{26}H_{21}N_3O$. Calculated, %: C 79.8; H 5.4; N 10.7. IR spectrum: 3425, 3340, 3300, 1710, and 1620 cm^{-1}

2-(3-Indolyl)-3-(5-bromo-3-oxindolyl)indole (XIV). Oxidation of VIII with hydrogen peroxide in alkali under conditions similar to those in method A gave XIV, with mp 306-307° and R_f 0.69, in 25% yield. Found, %: C 64.5; H 3.7; Br 18.7; N 9.5. $C_{24}H_{16}BrN_3O$. Calculated, %: C 65.1; H 3.6; Br 18.1; N 9.5. IR spectrum: 3330, 1700, and 1610 cm^{-1}. UV spectrum, λ_{max} (log ε): 219 (4.87), 259 (4.26), 289 (4.16) inflection, and 292 (4.09) nm (in methanol). Mass spectrum: M^+ 442.

2-(3-Indolyl)-3-(1-methyl-3-oxindolyl)indole (XV). This compound, with mp 301-302° and R_f 0.71, was obtained in 42% yield under conditions similar to those in method A by oxidation of VII with hydrogen peroxide in alkali. Found, %: C 79.4; H 5.1; N 10.5. $C_{25}H_{19}N_3O_4$. Calculated, %: C 79.5; H 5.1; N 11.1. IR spectrum: 1615, 1670, and 3370 cm^{-1}. UV spectrum, λ_{max} (log ε): 219 (4.81), 258 (4.09), 283 (4.08), and 292 nm (4.01).

2-(3-Indolyl)-2-hydroxy-3-indolinone (VI). An 0.12-g (0.005 mole) sample of hydrazine hydrate was added to a solution of 1.32 g (0.005 mole) of 3-(3-indolyl)dioxindole in 10 ml of methanol, and the mixture was refluxed for 15 min. It was then cooled to room temperature and acidified with glacial acetic acid. The precipitated 2-(3-indolyl)-2-hydroxy-3-indolinone was removed by filtration, washed with water, and crystallized from methanol to give 0.85 g of VI with mp 215-217° and R_f 0.5. Found, %: C 68.8; H 5.5; N 9.4. $C_{16}H_{12}N_2O_2 \cdot CH_3OH$. Calculated, %: C 68.8; H 5.4; N 9.5.

LITERATURE CITED

1. J. Bergman, Acta Chem. Scand., 25, 1277 (1971).

INDOLIZINES.

II.* SYNTHESIS AND PROPERTIES OF 2-METHYL(ARYL)-ETHOXY-CARBONYLINDOLIZINES

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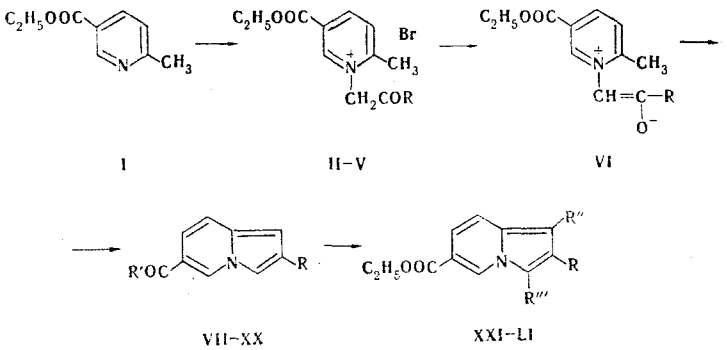
UDC 547.759.4.07

2-Substituted indolizine-6-carboxylic acids and their derivatives were synthesized. Their electrophilic substitution reactions are described.

We have previously described 2-alkyl(aryl)indolizine-7-carboxylic acids and their derivatives [1]. In a continuation of our research on the synthesis of indolizine derivatives with functional groups in various positions of the pyridine portion of the molecule, we synthe-

*See [1] for communication I.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 209-214, February, 1976. Original article submitted March 19, 1975.



II, VIII, XV—XVII R=C_6H_5; VII, XIII, XIV R=CH_3; III, IX R=p-$C_6H_4OCH_3$; X R=p-$C_6H_4CH_3$; IV, XI, XVIII R=p-C_6H_4Cl; V, VI, XII R=p-$C_6H_4NO_2$; XIX R=p-$C_6H_4NH_2$; XX R=p-$C_6H_4NHCOCH_3$; VII—XII, XIX, XX R′=OC_2H_5; XIII R′=NH_2; XV R′=OH; XIV, XVI, XVIII R′=$NHNH_2$; XVII R′=$NHNHSO_2C_6H_5$

sized derivatives of the previously unknown indolizine-6-carboxylic acids and investigated some nucleophilic and electrophilic substitution reactions of this group of substances.

Indolizines VII-LI were obtained via the above scheme.

The R, R", and R"' values for XXI-LI are presented in Table 1.

2-Methyl-5-ethoxycarbonylpyridine (I) is converted to quaternary salts II-V by reaction with bromoacetone and phenacyl bromides. On treatment with ammonium hydroxide the salts for which R = C_6H_5 are converted to unstable anhydro bases. On standing in air or in a vacuum desiccator the compounds undergo a color change from bright red to bright yellow; this is associated with their spontaneous cyclization to indolizines VIII-XII. The rate of cyclization of the anhydro bases is determined by the character of R. This process takes place most rapidly (in about 24 h) when R = C_6H_5. When there are substituents in the phenyl ring, the anhydro bases are cyclized at room temperature most slowly, but the reaction is accelerated considerably when the reagents are heated in alcohols or in dimethylformamide (DMF). Anhydro base VI proved to be stable at 20° only when there was a strong electron-acceptor nitro group in the ring.

We were unable to synthesize 2-methyl-6-ethoxycarbonylindolizine (VII) by the method described above. The anhydro base formed on treatment of 1-acetonyl-2-methyl-5-ethoxycarbonylpyridinium bromide with ammonium hydroxide is converted extremely rapidly to an indolizine derivative with simultaneous formation of the corresponding amide: 2-Methylindolizine-6-carboxamide (XIII) precipitates from the reaction solution in practically quantitative yield 10 min after mixing the reagents at 5-10°. We were able to obtain indolizine VII by heating the appropriate pyridinium salt in absolute ethanol in the presence of sodium bicarbonate.

Indolizines VII, VIII, and XI are converted to 2-substituted indolizine-6-carboxylic acid hydrazides by brief (4 h) heating with a 10- to 20-fold (by weight) amount of hydrazine hydrate. However, the reaction does not go to completion when the indolizines are heated with a small excess of hydrazine hydrate in alcohol, and this constitutes evidence for the reduced (as compared with pyridinecarboxylic acid esters) reactivity of the ethoxycarbonyl group of indolizines in nucleophilic reactions. This is also confirmed by the negative results obtained in an attempt to subject indolizine VII to reaction with phenylmagnesium bromide and phenyllithium.

On the other hand, the electrophilic substitution of indolizines VII-XII proceeds readily, and depending on the reagent, the character of the substituent in the 2 position of the indolizine molecule, and the reaction temperature conditions, 3-mono- or 1,3-disubstituted products are formed.* Indolizines VII-XII are readily acylated in the 3 position on heating with excess acetic anhydride or aromatic acid chlorides. Indolizine VII, in which, owing to the donor character of the substituent attached to $C_{(2)}$, the electron density on the carbon atoms of the pyrrole ring is increased as compared with indolizines VIII-XII, is benzoylated by benzoyl chloride in the presence of triethylamine at room temperature, whereas when it is heated with acid anhydrides or chlorides it reacts extremely vigorously with resinification of the reaction products, which hinders their isolation.

*The structures of these compounds were established on the basis of PMR spectral data. A more detailed discussion of the spectra will be presented in one of our subsequent communications.

TABLE 1. Conditions for the Preparation of Indolizine Derivatives XXI-LI and Their Physical Characteristics

Compound	R	R″	R‴	Method	Reaction time, h	mp, °C	Crystallization solvent	Empirical formula	Found, %			Calc., %			Yield, %
									C	H	N	C	H	N	
XXI	CH_3	CHO	CHO	A	1	122—124	Ether–petroleum ether	$C_{14}H_{13}NO_4$	64,9	5,1	5,0	64,9	5,1	5,4	47
XXII	C_6H_5	H	CHO	A	1	146—148	2-Propanol	$C_{18}H_{15}NO_3$	73,6	5,2	—	73,7	5,1	—	90,5
XXIII	p-$C_6H_4OCH_3$	H	CHO	A	1	115—116	2-Propanol	$C_{19}H_{17}NO_4$	70,7	5,4	—	70,6	5,3	—	73,8
XXIV	p-$C_6H_4CH_3$	H	CHO	A	1	121—123	2-Propanol	$C_{19}H_{17}NO_3$	73,8	5,7	—	74,3	5,6	—	68
XXV	p-C_6H_4Cl	H	CHO	A	4	128—130	Ethanol	$C_{18}H_{14}ClNO_3$	66,0	4,5	10,9[a]	66,0	4,3	10,8[a]	91
XXVI	C_6H_5	H	$COCH_3$	B	10	182—184	Ethanol	$C_{19}H_{17}NO_3 \cdot {}^1/_2H_2O$	72,0	5,7	—	72,1	5,7	—	69
XXVII	p-$C_6H_4OCH_3$	H	$COCH_3$	B	10	113—115	2-Propanol	$C_{20}H_{19}NO_4$	70,7	5,4	—	71,1	5,6	—	87,5
XXVIII	p-$C_6H_4CH_3$	H	$COCH_3$	B	7	137—139	2-Propanol	$C_{20}H_{19}NO_3$	74,4	5,8	—	74,7	5,9	—	56
XXIX	p-C_6H_4Cl	H	$COCH_3$	C	10	145—147	Heptane	$C_{19}H_{16}ClNO_3$	66,9	4,7	10.2a	66,8	4,7	10,4[a]	43,8
XXX	p-$C_6H_4NO_2$	H	$COCH_3$	C	35	202—203	Ethyl acetate	$C_{19}H_{16}N_2O_5$	64,7	4,6	8,3	64,8	4,6	8,0	57
XXXI	p-$C_6H_4NH_2$	H	$COCH_3$	—	—	122—124	Ether	$C_{19}H_{18}N_2O_3$	70,7	5,5	8,5	70,8	5,6	8,7	58
XXXII	CH_3	H	COC_6H_5	E	72	141—143	Ether–benzene	$C_{19}H_{17}NO_3$	74,5	5,5	—	74,3	5,5	—	66,4
XXXIII	CH_3	H	p-COC_6H_4Cl	E	48	205—206	Ether–benzene	$C_{19}H_{16}ClNO_3$	66,5	4,8	10,1[a]	66,8	4,7	10,3a	43,5
XXXIV	C_6H_5	H	COC_6H_5	D	3	145—147	2-Propanol	$C_{24}H_{19}NO_3$	77,7	5,3	—	78,0	5,2	—	70,3
XXXV	p-$C_6H_4OCH_3$	H	COC_6H_5	D	3	121—122	Heptane–2-propanol	$C_{25}H_{21}NO_4$	75,7	5,4	3,6	75,4	5,3	3,5	37
XXXVI	p-C_6H_4Cl	H	COC_6H_5	D	4	190—192	Ethanol	$C_{24}H_{18}ClNO_3$	71,3	4,9	8,7[a]	71,4	4,5	8,8a	94
XXXVII	p-$C_6H_4NO_2$	H	COC_6H_5	D	1	243—244	Dimethylformamide	$C_{24}H_{18}N_2O_5$	69,8	4,6	6,9	69,6	4,3	6,8	82,5
XXXVIII[b]	p-$C_6H_4NH_2$	H	COC_6H_5	—	—	277—278	Ethanol–ethyl acet.	$C_{24}H_{20}N_2O_3$	73,6	5,7	7,3	73,3	5,4	7,1	82
XXXIX c	CH_3	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	F	8	190—192	–	$C_{18}H_{27}N_3O_2 \cdot 2C_4H_6O_6 \cdot H_2O$	47,9	6,5	—	47,7	6,6	—	40,7
XL	C_6H_5	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	F	16	158—160	2-Propanol	$C_{23}H_{29}N_3O_2 \cdot 2HCl$	59,5	7,0	15,1[a]	59,8	6,9	15,3[a]	57,6
XLI	p-$C_6H_4OCH_3$	H	$CH_2N(CH_3)_2$	F	6	125—127	Acetone	$C_{21}H_{21}N_2O_3 \cdot HCl \cdot H_2O$	62,4	6,2	9,3[a]	62,0	6,2	8.8[a]	53,5
XLII	o-$C_6H_4CH_3$	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	F	16	85—86	Acetone–2-propanol	$C_{24}H_{31}N_2O_2 \cdot 2HCl \cdot H_2O$	59,9	7,2	14,9[a]	59,5	7,3	14,6	48,2
XLIII	p-C_6H_4Cl	H	$CH_2N(CH_3)_2$	F	16	62—64	Heptane	$C_{20}H_{21}ClN_2O_3$	67,2	6,0	7,9	67,3	5,9	7,9	76
XLIV	p-$C_6H_4NO_2$	H	$CH_2N(CH_3)_2$	F	30	92—94	Hexane	$C_{20}H_{21}N_3O_4$	65,5	5,7	11,3	65,4	5,8	11.4	47.2
XLV	p-$C_6H_4NO_2$	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	F	3	142—143	Ether–ethyl acetate	$C_{23}H_{28}N_4O_4$	64,8	6,6	13,2	65,1	6,7	13,2	68,5
XLVI	CH_3	H	NO	G	1	130—132	2-Propanol	$C_{12}H_{12}N_2O_3$	62,2	5,3	—	62,1	5,2	—	43,8
XLVII	C_6H_5	H	NO	G	1	169—170	2-Propanol	$C_{17}H_{14}N_2O_3$	69,1	4,8	9,4	69,3	4,8	9,5	72
XLVIII	p-$C_6H_4OCH_3$	H	NO	G	1	171—172	2-Propanol	$C_{18}H_{16}N_2O_4$	66,6	4,9	8,9	66,6	5,0	8,7	73
XLIX	p-$C_6H_4CH_3$	H	NO	G	1	160—161	2-Propanol	$C_{18}H_{16}N_2O_3 \cdot {}^1/_2H_2O$	68,3	5,2	8,8	68,1	5,4	8,8	72,5
L	p-C_6H_4Cl	H	NO	G	1	190—191	Dimethylformamide	$C_{17}H_{13}ClN_2O_3$	61,9	3,9	8,4	62,1	4,0	8,5	79
LI	p-C_6H_4Cl	H	NH_2	—	—	143—145	Ethanol	$C_{17}H_{15}ClN_2O_2$	64,7	4,8	9,0	64,9	4,8	8,9	31,6

a) Analysis for chlorine.

b) Obtained by the method used to prepare XIX.

c) Ditartrate.

The nitrosation of VII-XII was accomplished by reaction with isoamyl nitrite, formylation was realized by reaction with phosphorus oxychloride in DMF, and the Mannich reaction was accomplished by heating with bis(dimethylamino)methane. Just as in acylation, only 3-monosubstituted indolizines were obtained by nitrosation. On the other hand, the formation of both 3-mono- and 1,3-disubstituted indolizines was observed in the Vilsmeier and Mannich reactions. Thus 2-methyl-1,3-diformyl-6-ethoxycarbonylindolizine (XXI) was obtained from the most reactive indolizine (VII), whereas indolizines VIII-XI with aryl groups in the 2 position are converted only to monoformyl derivatives (XXII-XXV). Under the same conditions, indolizines VII, VIII, and X on heating with bis(dimethylamino)methane (at 100°) form 1,3-bis(dimethylaminomethyl) derivatives (XXXIX, XL, and XLII), whereas the less reactive indolizines XI and XII give 3-dimethylaminomethyl derivatives (XLIII and XLIV). When the temperature is raised to 150°, XII is converted to 1,3-disubstituted XLV. Indolizines with one and two dimethylaminomethyl groups form salts — hydrochlorides and tartrates. Salts of indolizines with one basic group are hydrolyzed in aqueous solution at room temperature at an appreciable rate with splitting out of the dimethylaminomethyl groups: A few minutes after dissolving the salts in water, 3-unsubstituted indolizines precipitate. Salts of indolizines with two basic groups (XL, XLII) are stable in aqueous solutions on prolonged standing. Indolizines XIX and LI, obtained by reduction of the corresponding nitro (XII) and nitroso derivatives (L), form hydrochlorides that are readily hydrolyzed in aqueous solutions.

EXPERIMENTAL

1-Phenacyl-2-methyl-5-ethoxycarbonylpyridinium Bromide (II). A mixture of 10 g (60 mmole) of 2-methyl-5-ethoxycarbonylpyridine (I) and 12 g (60 mmole) of phenacyl bromide in 30 ml of acetone was refluxed for 6 h,* after which the precipitate was formed by filtration and washed with acetone to give 18 g (82%) of a product with mp 178-180° (from ethanol). Found, %: C 56.1; H 4.9; Br 22.0. $C_{17}H_{18}BrNO_3$. Calculated, %: C 56.1; H 5.0; Br 21.9.

1-(p-Chlorophenacyl)-2-methyl-5-ethoxycarbonylpyridinium Bromide (IV). This compound, with mp 158-160° (from acetone—ethanol), was similarly obtained in 88% yield. Found, %: Br + Cl 29.1. $C_{17}H_{17}BrClNO_3$. Calculated, %: Br + Cl 29.0.

1-(p-Nitrophenacyl)-2-methyl-5-ethoxycarbonylpyridinium Bromide (V). A mixture of 15 g (91 mmole) of I and 22.2 g (91 mmole) of p-nitrophenacyl bromide in 45 ml of acetone was refluxed for 10 h, after which the solution was vacuum evaporated, and the residue was triturated successively with ether and acetone to give 24.2 g (65%) of a product with mp 113-115° (from 2-propanol). Found, %: Br 18.9, N 6.4. $C_{17}H_{17}BrN_2O_5 \cdot H_2O$. Calculated, %: Br 18.7; N 6.6.

1-(p-Methoxyphenacyl)-2-methyl-5-ethoxycarbonylpyridinium Bromide (III). This compound, with mp 141-143° (from ethanol), was obtained as in the preceding experiment in 54% yield. Found, %: C 54.2; H 5.3; Br 20.3. $C_{18}H_{20}BrNO_4$. Calculated, %: C 54.8; H 5.1; Br 20.2.

1-(p-Nitrophenacyl)-2-methyl-5-ethoxycarbonylpyridinium Anhydro Base (VI). A 20-ml sample of 25% ammonium hydroxide was added with cooling to a solution of 10 g (24.3 mmole) of V in 200 ml of water, and the resulting dark-red precipitate was removed by filtration and washed with water to give 7.3 g (90.5%) of product. Found, %: N 8.9. $C_{17}H_{16}N_2O_5$. Calculated, %: N 8.5.

2-Methyl-6-ethoxycarbonylindolizine (VII). A solution of 10 g (60 mmole) of I and 8.2 g (60 mmole) of bromoacetone in 20 ml of acetone was refluxed for 6 h, after which the acetone was removed by vacuum distillation, and the residue was triturated with ether and dissolved in 200 ml of absolute ethanol. The alcohol solution was refluxed for 2 h in the presence of 10.3 g (123 mmole) of sodium bicarbonate, after which the mixture was filtered, and the alcohol was removed by vacuum distillation. The residue was extracted with ether, and the material in the ether extract was vacuum sublimated at 0.6 mm to give 7.3 g (59%) of a product with mp 70-71°. Found, %: C 70.7; H 6.4; N 7.0. $C_{12}H_{13}NO_2$. Calculated, %: C 70.6; H 6.5; N 6.9.

2-Methylindolizine-6-carboxamide (XIII). 1-Acetonyl-2-methyl-5-ethoxycarbonylpyridinium bromide, obtained as described above, was dissolved in 200 ml of water, after which 30 ml of 25% ammonium hydroxide was added, and the resulting precipitate was removed by filtration to give 9.2 g (87%) of a product with mp 198-200° (from methanol). Found, %: C 68.8; H 5.6; N 16.1. $C_{10}H_{10}N_2O$. Calculated, % C 68.9; H 5.7; N 16.1.

*The end of the reaction in all cases was determined by chromatography on Silufol UV-254 plates.

2-Phenyl-6-ethoxycarbonylindolizine (VIII). A total of 40 ml of 25% ammonium hydroxide was added with cooling to a solution of 18.2 g (50 mmole) of II in 300 ml of water, and the resulting orange-red precipitate of the anhydro base was removed by filtration after 30 min, during which the color of the precipitate changed to orange. After standing in the air for 15 h, the precipitate took on a light-yellow color, and this constituted evidence for the conversion of the anhydro base to the indolizine derivative. The product before and after recrystallization from 2-propanol had the same chromatographic lability. The yield of product with mp 148-150° was 10.5 g (79%). Found, %: C 76.8; H 5.5; N 5.3. $C_{17}H_{15}NO_2$. Calculated, %: C 77.0; H 5.7; N 5.2.

The following compounds were obtained by the method used to prepare indolizine VIII (to complete the cyclization, the anhydro base was refluxed with 2-propanol for from 25 min to 4 h).

2-(p-Methoxyphenyl)-6-ethoxycarbonylindolizine (IX). This compound, with mp 163-165° (from DMF), was obtained in 61.5% yield. Found, %: C 73.3; H 5.7; N 4.9. $C_{18}H_{17}NO_3$. Calculated, %: C 73.2; H 5.8; N 4.8.

2-(p-Tolyl)-6-ethoxycarbonylindolizine (X). This compound, with mp 158-160° (from DMF), was obtained in 65% yield. Found, %: C 77.5; H 6.2; N 5.0. $C_{18}H_{17}NO_2$. Calculated, %: C 77.6; H 6.1; N 5.0.

2-(p-Chlorophenyl)-6-ethoxycarbonylindolizine (XI). This compound, with mp 147-148° (from ethanol), was obtained in 78% yield. Found, %: C 68.1; H 4.8; Cl 11.8. $C_{17}H_{14}ClNO_2$. Calculated, %: C 68.1; H 4.7; Cl 11.8.

2-(p-Nitrophenyl)-6-ethoxycarbonylindolizine (XII). This compound, with mp 187-188° (from ethanol—DMF), was obtained in 97% yield. Found, %: C 65.8; H 4.6; N 8.9. $C_{17}H_{14}N_2O_4$. Calculated, %: C 65.8; H 4.5; N 9.0.

2-(p-Aminophenyl)-6-ethoxycarbonylindolizine (XIX). A 3.5-ml sample of hydrazine hydrate was added to a refluxing solution of 2 g (6.4 mmole) of indolizine XII in 150 ml of dioxane containing 0.5 g of palladium on carbon, after which the mixture was heated for another 40 min. The catalyst was then separated, and the solution was vacuum evaporated to give 1.2 g (66.5%) of a product with mp 178-180° (from ethanol). Found, %: C 72.8; H 5.8; N 10.3. $C_{17}H_{16}N_2O_2$. Calculated, %: C 72.8; H 5.8; N 10.0.

2-(p-Acetaminophenyl)-6-ethoxycarbonylindolizine (XX). A mixture of 1 g (3.5 mmole) of XIX and 2 ml of acetic anhydride in 40 ml of chloroform was allowed to stand at 20° for 24 h. Workup gave 0.85 g (74%) of a product with mp 221-222° (from dioxane). Found, %: C 70.3; H 5.9; N 8.3. $C_{19}H_{18}N_2O_3$. Calculated, %: C 70.8; H 5.6; N 8.7.

2-Phenylindolizine-6-carboxylic Acid (XV). A suspension of 2 g (7.5 mmole) of indolizine VIII in 20 ml of concentrated HCl was refluxed for 14 h, after which the precipitate was removed by filtration to give 1.5 g (84%) of a product with mp 235-237° (from ethanol). Found, %: C 75.7; H 4.7. $C_{15}H_{11}NO_2$. Calculated, %: C 75.9; H 4.7.

2-Methylindolizine-6-carboxylic Acid Hydrazide (XIV). A suspension of 1 g (5 mmole) of indolizine VII in 20 ml of hydrazine hydrate was refluxed for 4 h, after which the precipitate was removed by filtration and washed with water to give 0.6 g (64.6%) of a product with mp 159-160° (from chloroform). Found, %: C 63.1; H 5.8; N 22.3. $C_{10}H_{11}N_3O$. Calculated, %: C 63.5; H 5.8; N 22.2.

2-Phenylindolizine-6-carboxylic Acid Hydrazide (XVI). This compound, with mp 232-234°, was obtained in 95% yield by the method used to prepare hydrazide XIV. Found, %: C 71.7; H 5.2; N 16.5. $C_{15}H_{13}N_3O$. Calculated, %: C 71.7; H 5.2; N 16.7.

2-(p-Chlorophenyl)indolizine-6-carboxylic Acid Hydrazide (XVIII). This compound, with mp 231-233°, was obtained in 61.5% yield by the method used to prepare hydrazide XIV. Found, %: Cl 12.3; N 14.4. $C_{15}H_{12}ClN_3O$. Calculated, %: Cl 12.4; N 14.7.

2-Phenylindolizine-6-carboxylic Acid Benzenesulfonylhydrazide (XVII). A 2.7-g (15.7) mmole) sample of benzenesulfonyl chloride was added to a solution of 3.6 g (14.3 mmole) of hydrazide XVI in 50 ml of pyridine, after which the mixture was allowed to stand at 20° for 20 h. The pyridine was then removed by distillation, the residue was poured into 100 ml of water, and the resulting crystals were removed by filtration to give 4.7 g (84%) of a product with mp 238-240° (from acetone). Found, %: C 64.6; H 4.7; N 10.5; S 7.9. $O_{21}H_{17}N_3O_3S$. Calculated, %: C 64.4; H 4.4; N 10.3; S 8.2.

Electrophilic Substitution Reactions. Method A. An 0.76-g (5 mmole) sample of phosphorus oxychloride was added at 0° to 1.6 g of DMF, after which the solution was allowed to stand at 18-20° for 15 min. It was then cooled to 2-5°, and a solution of 5 mmole of indolizine derivative VII-XI in 30 ml of DMF was added, and the mixture was stirred at 20° for 4 h. It was then poured over ice, the resulting mixture was neutralized with 2 N sodium hydroxide solution, and the precipitate was removed by filtration.

Method B. A solution of 7.5 mmole of indolizine derivative VIII-X in 20 ml of acetic anhydride was refluxed for 10 h, after which the mixture was cooled and poured into ice water. The resulting precipitate was removed by filtration and recrystallized.

Method C. The acetylation of VIII and IX was carried out by method B. The reaction solution was vacuum evaporated, and the residue was made alkaline with 25% potassium carbonate solution and extracted with chloroform.

Method D. A solution of 10 mmole of indolizine derivative VIII, IX, XI, or XII in 15 ml of benzoyl chloride was heated at 70-75° for 3 h, after which it was cooled and poured into 150 ml of petroleum ether. The mixture was then allowed to stand at 4° for 20 h, and the precipitated crystals were separated.

Method E. A mixture of 5 mmole of indolizine VII, 5 mmole of the acid chloride, and 5 mmole of triethylamine was allowed to stand at 20° for 3 days, after which 10 ml of water was added, and the mixture was extracted with benzene. The benzene solution was evaporated, and the residue was crystallized.

Method F. A mixture of 5 mmole of indolizine derivative VII-XII, 15 mmole of bis(dimethylamino)methane, and 25 ml of dioxane was refluxed for 8 h. In the case of XXXIX the solution was vacuum evaporated, the residue was extracted with ether, the ether solution was evaporated, the residue was dissolved in ethanol, and the ethanol solution was treated with 10 mmole of tartaric acid. In the case of XLIII and XLIV, the bases were isolated from ether solution. Compound XLV was obtained by refluxing the components in DMF.

Method G. A 1.4-ml sample of a 25% alcohol solution of hydrogen chloride was added to a solution of 5 mmole of indolizine derivative VII-XI in 100 ml of DMF, after which the solution was cooled and treated with 7.5 mmole of isoamyl nitrite. The mixture was allowed to stand at 20° for 1 h, after which it was poured into 200 ml of water, and the resulting precipitate was removed by filtration.

2-(p-Aminophenyl)-3-acetyl-6-ethoxycarbonylindolizine (XXXI). A suspension of 1.8 g (4.8 mmole) of XXX and 1.3 g of Raney nickel in 100 ml of ethanol was shaken with hydrogen. After 3 moles of hydrogen had been absorbed, the catalyst was removed by filtration, the alcohol was removed by vacuum distillation, and the residue was extracted with hot ether.

2-(p-Chlorophenyl)-7-amino-6-ethoxycarbonylindolizine (LI). A 1-ml sample of hydrazine hydrate was added dropwise with vigorous stirring to a refluxing solution of 1 g (3 mmole) of L in 20 ml of ethanol containing 0.3 g of 5% palladium on carbon. After gas evolution has ceased (about 15 min), the mixture was filtered rapidly, and the filtrate was vacuum evaporated at no higher than 50°.

The synthetic methods, reaction times, yields, melting points, and the results of elementary analysis of XXI-LI are presented in Table 1.

LITERATURE CITED

1. E. E. Mikhlina, A. D. Yanina, T. S. Loseva, K. F. Turchin, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., 977 (1974).