INDOLIZINES.

# V.* SYNTHESIS AND PROPERTIES OF 2-METHYL(ARYL)-8-CARBETHOXY-INDOLIZINES

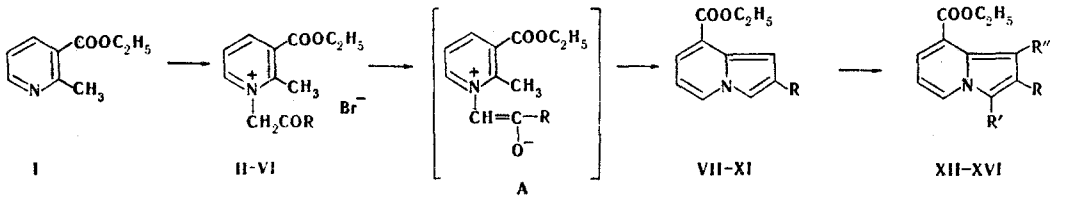
T. S. Loseva, M. S. Goizman, L. M. Alekseeva,
O. R. Shvarts, E. E. Mikhlina, and L. N. Yakhontov

UDC 547.759.4.07:543.422.25

2-Methyl(aryl)-8-carbethoxyindolizines were synthesized, and their reactivities with respect to several nucleophilic and electrophilic reagents were studied. The structures of derivatives of 8-carbethoxyindolizines and the protonation centers were determined by PMR spectroscopy. The ionization constants were measured by potentiometric titration.

2-Methyl(aryl)indolizine-6(7)-carboxylic acids and their derivatives were described in previous communications [2-4]. The synthesis of 2-substituted indolizine-8-carboxylic acids and the study of some of their nucleophilic and electrophilic reactions constituted a continuation of the investigation of indolizines with functional groups in various positions of the pyridine ring.

Indolizines VII-XVI (Table 1) were obtained via the following scheme:




The reaction of 2-methyl-3-carbethoxypyridine (I) with bromoacetone and phenacyl bromides gives quaternary salts II-VI. Anhydro bases A, which are bright-orange crystalline substances, are formed by treatment of salts III-VI with ammonium hydroxide. Their color changes to light-brown when they are allowed to stand in the air, and this constitutes evidence for spontaneous cyclization to indolizine derivatives. This transformation is accelerated substantially when the anhydro bases are heated briefly in organic solvents; the products in this case were 2-aryl-8-carbethoxyindolizines (VIII-XI, Table 1). Because of their instability, anhydro bases A could not be isolated in pure form. The reactivities of these compounds are similar to the reactivities of the anhydro bases obtained from 1-phenacyl-2-methyl-5-carbethoxypyridinium bromides [3] but differ substantially from the reactivities of the anhydro bases isolated in the case of 1-phenacyl-2-methyl-4-carbethoxypyridinium bromides [2, 4]. In comparison with their isomers, the latter are characterized by considerable resistance to conversion to indolizine derivatives under the usual conditions and remain unchanged during prolonged storage.

2-Methyl-8-carbethoxyindolizine (VII) was obtained in 68% yield by another method by treating 1-(2-oxopropyl)-2-methyl-3-carbethoxypyridinium bromide (II) in alcohol in the presence of sodium bicarbonate. The synthesis of this compound in 30% yield by the classical Chichibabin method (by the brief heating of an aqueous solution of the quaternary salt in the presence of sodium bicarbonate) was described in [5].

When indolizines VIII-X are refluxed briefly (4-5 h) in excess hydrazine hydrate, they are converted to 2-arylindolizine-8-carboxylic acid hydrazides in greater than 80% yields. We were unable to obtain a hydrazide in the case of 2-(p-nitrophenyl)-substituted indolizine

*See [1] for communication IV.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 802-808, June, 1978. Original article submitted July 11, 1977.

TABLE 1. 3-Substituted 2-Methyl(aryl)-8-carbethoxyindolizines XII-XVI

| Compound | R | R′ | R″ | Method | Reaction time, h | mp, °C | Found, % | | | Empirical formula | Calc., % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N | | C | H | N | |
| XIIa | $CH_3$ | $COCH_3$ | H | A | 10 | 108—110[a] | 68,5 | 6,2 | 5,9 | $C_{14}H_{15}NO_3$ | 68,5 | 6,1 | 5,7 | 68 |
| XIIb | $CH_3$ | CHO | H | B | 2 | 80—82[b] | 67,6 | 5,7 | — | $C_{13}H_{13}NO_3$ | 67,5 | 5,6 | — | 53 |
| XIIc | $CH_3$ | $COC_6H_5$ | H | C | 2 | 75—76[a] | 74,1 | 5,5 | 4,6 | $C_{19}H_{17}NO_3$ | 74,2 | 5,5 | 4,5 | 75 |
| XIId | $CH_3$ | NO | H | D | 1 | 92—94[b] | 62,3 | 5,1 | 12,0 | $C_{12}H_{12}N_2O_3$ | 62,0 | 5,2 | 12,0 | 77 |
| XIIIa | $C_6H_5$ | $COCH_3$ | H | A | 10 | 55—57[b] | 74,5 | 5,7 | — | $C_{19}H_{17}NO_3$ | 74,3 | 5,5 | — | 69 |
| XIIIb | $C_6H_5$ | $COC_6H_5$ | H | C | 2 | 114—115[c] | 78,1 | 5,3 | — | $C_{24}H_{19}NO_3$ | 78,0 | 5,2 | — | 86 |
| XIIIc | $C_6H_5$ | NO | H | D | 1 | 120—122[b] | 69,7 | 4,9 | 9,6 | $C_{17}H_{14}N_2O_3$ | 69,4 | 4,8 | 9,5 | 82 |
| XIIId | $C_6H_5$ | $CH_2N(CH_3)_2$ | H | E | 10 | 85—86 | 56,4 | 6,1 | 5,5 | $C_{20}H_{22}N_2O_2 \cdot C_4H_6O_6 \cdot 2H_2O$[d] | 56,6 | 6,3 | 5,5 | 57 |
| XIVa | $C_6H_4CH_3$-*p* | $COCH_3$ | H | A | 10 | 99—101[b] | 74,8 | 6,1 | — | $C_{20}H_{19}NO_3$ | 74,7 | 5,9 | — | 62 |
| XIVb | $C_6H_4CH_3$-*p* | $COC_6H_5$ | H | C | 2 | 108—110[b] | 68,9 | 5,9 | — | $C_{25}H_{21}NO_3 \cdot 3H_2O$ | 68,6 | 6,2 | — | 66 |
| XIVc | $C_6H_4CH_3$-*p* | NO | H | D | 1 | 114—115[b] | 70,3 | 5,4 | 9,2 | $C_{18}H_{16}N_2O_3$ | 70,1 | 5,5 | 9,1 | 85 |
| XIVd | $C_6H_4CH_3$-*p* | $CH_2N(CH_3)_2$ | H | E | 10 | 68—70 | 59,4 | 6,6 | 5,1 | $C_{21}H_{24}N_2O_2 \cdot C_4H_6O_6 \cdot H_2O$[d] | 59,5 | 6,4 | 5,5 | 71 |
| XIVe | $C_6H_4CH_3$-*p* | $C_5H_{10}NO$[e] | $C_5H_{10}NO$[e] | F | 72 | 73—75 | 52,8 | 5,9 | 5,5 | $C_{28}H_{35}N_3O_4 \cdot 2C_4H_6O_6$[d] | 53,1 | 6,2 | 5,2 | 77 |
| XVa | $C_6H_4OCH_3$-*p* | $COCH_3$ | H | A | 14 | 120—122[b] | 71,1 | 5,4 | 4,0 | $C_{20}H_{19}NO_4$ | 71,2 | 5,7 | 4,1 | 35 |
| XVb | $C_6H_4OCH_3$-*p* | CHO | H | B | 2 | 100—102[b] | 70,5 | 5,4 | 4,2 | $C_{19}H_{17}NO_4$ | 70,5 | 5,3 | 4,3 | 45 |
| XVc | $C_6H_4OCH_3$-*p* | $COC_6H_5$ | H | C | 2 | 135—136[b] | 75,1 | 5,3 | — | $C_{25}H_{21}NO_4$ | 75,2 | 5,1 | — | 63 |
| XVd | $C_6H_4OCH_3$-*p* | NO | H | D | 1 | 135—136[b] | 66,3 | 4,8 | 8,9 | $C_{18}H_{16}N_2O_4$ | 66,6 | 5,0 | 8,9 | 63 |
| XVe | $C_6H_4OCH_3$-*p* | $C_5H_{10}NO$[e] | $C_5H_{10}NO$[e] | F | 23 | 188—190[f] | 67,9 | 7,4 | 8,4 | $C_{28}H_{35}N_3O_5$ | 68,1 | 7,1 | 8,5 | 56 |
| XVIa | $C_6H_4NO_2$-*p* | $COC_6H_5$ | H | C | 2 | 156—158[b] | 68,6 | 4,3 | 6,8 | $C_{24}H_{18}N_2O_5$ | 68,7 | 4,3 | 6,7 | 60 |
| XVIb | $C_6H_4NO_2$-*p* | NO | H | D | 1 | 209—210[b] | 60,0 | 3,9 | 12,5 | $C_{17}H_{13}N_3O_5$ | 60,2 | 3,8 | 12,3 | 87 |
| XVIc | $C_6H_4NO_2$-*p* | $CH_2N(CH_3)_2$ | H | E | 8 | 108—110[b] | 65,6 | 5,9 | 11,4 | $C_{20}H_{21}N_3O_4$ | 65,5 | 5,7 | 11,5 | 68 |
| XVId | $C_6H_4NO_2$-*p* | $C_5H_{10}NO$ | H | F | 23 | 170—172[f] | 64,2 | 5,7 | 10,2 | $C_{22}H_{23}N_3O_5$ | 64,0 | 5,6 | 10,2 | 81 |

a) From ether. b) From isopropyl alcohol. c) From benzene. d) Tartrate. e) Morpholinomethyl. f) From ethyl acetate.

XI even when the components were refluxed for a long time (42 h) or when a mixture of the substances was refluxed in DMF.

The reaction of indolizines VIII and X with phenyllithium was studied. In the first case (2-phenyl-8-indolizinyl)diphenylmethanol was isolated along with the starting compound, while in the second case starting X was recovered. The low reactivity of the ester group in 2-aryl-8-carbethoxyindolizines was noted not only under the conditions of the organometallic synthesis but also in reactions with other nucleophilic reagents (for example, with ammonia). Prolonged (40 h) shaking of indolizine VIII with 25% ammonium hydroxide and prolonged (3 months) standing of a solution of VIII in a 25% solution of ammonia in alcohol did not lead to 2-phenylindolizine-8-carboxamide.

As in the case of the previously described isomeric 2-substituted indolizine-6- and -7-carboxylic acids, electrophilic substitution proceeds readily in the case of indolizines VII-XI and leads to 3-monosubstituted (and in some cases 1,3-disubstituted) compounds. Indolizines VII-IX are acylated in the 3 position when they are heated with excess acetic anhydride. In the case of X and XI the reaction mixtures contained the starting compounds and considerable amounts of resinous products even after prlonged (14-20 h) refluxing in acetic anhydride. We were able to isolate only 2-(p-methoxyphenyl)-3-acetyl-8-carbethoxyindolizine (XVa) in the individual state.

The benzoylation of indolizines VII-XI was accomplished with benzoyl chloride in benzene or in excess reagent at room temperature, by heating, and in the presence of triethylamine. Reaction at room temperature gives the best results.

The Vilsmeier reaction proceeded successfully only in the case of VII and X, and 3-formylindolizines XIIb and XVb were obtained. An increase in the reaction time at 0°C from 2 h to 5 days and reaction at 20°C did not lead to positive results: in all cases the reaction did not go to completion, and this hindered the isolation of the individual formyl derivatives.

The nitrosation of indolizines VII-XI with isoamyl nitrite in DMF proceeds readily to give 3-nitroso derivatives. In the case of the reaction of VIII-XI with Mannich reagents — heating with bis(dimethylamino)methane and reaction with morpholine and formalin at room temperature — only 3-(dimethylaminomethyl) derivatives XIIId, XIVd, and XVIc are formed in the first case, and either 1,3-bis(morpholinomethyl) derivatives XIVe and XVe or 3-mono(morpholinomethyl) derivative XVId are formed in the second case, depending on the character of the substituent attached to $C_{(2)}$.

The hindrance to some electrophilic substitution reactions observed for 2-(p-nitrophenyl)-8-carbethoxyindolizine (XI) is evidently associated with the effect of the strong electron-acceptor p-nitrophenyl substituent, which reduces the electron density in the pyrrole ring substantially.

The position of the substituents introduced in the reaction of VII-XI with electrophilic reagents was established by means of the PMR spectra (Table 2). The assignment of the signals of the protons for VII-IX and XI was made on the basis of the character of their multiplicity. Thus the broad singlet at 6.83 ppm in the spectrum of VII was assigned to the 1-H proton; the 3-H proton appears as a quintet ($J_{2\text{-}CH_3,1\text{-}H}$ = 0.9 Hz; $J_{13} \approx 1.2$ Hz) at 6.98 ppm. The signal of the 6-H proton, which has the form of a triplet ($J_{56} = J_{67} = 7$ Hz), occupies the strongest-field position (6.25 ppm) relative to the signals of both the pyrrole and pyridine fragments of the molecule. The quartet at 7.39 ppm was assigned to the 7-H proton ($J_{67} = 7$ Hz; $J_{57} = 0.9$ Hz); the signal of the 5-H proton is observed in the form of a doublet of triplets ($J_{56} = 7$ Hz, $J_{57} = J_{15} = 0.9$ Hz) at 7.8 ppm. When electronegative substituents (XIIa, c, d, XIIIa, c, and XVIa) are introduced, the signals of the 1-, 5-, 6-, and 7-H protons are shifted to the weak-field region as compared with the signals of these protons in the spectra of starting VII-IX and XI. However, whereas the shift does not exceed 1 ppm for the 1-, 6-, and 7-H signals, it reaches 2.15-2.67 ppm for 5-H. This pronounced shift of the 5-H signals is evidently associated with the deshielding effect of the magnetically anisotropic substituents attached to the $C_{(3)}$ atom.

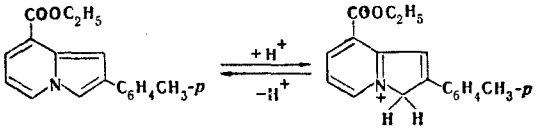
Signals of the protons of the morpholinomethylene substituent are observed along with the signals of the aromatic protons in the stronger-field region of the spectra of XVId and XVe. Thus the 1-$CH_2$ and 3-$CH_2$ signals appear in the spectrum of XVe in the form of singlets at 3.65 and 3.85 ppm, respectively.

TABLE 2. Chemical Shifts in the PMR Spectra of the Neutral Molecules and Cations of 2-Methyl(aryl)-8-carbethoxyindolizines*

| Compound | Solvent | δ, ppm | | | | |
|---|---|---|---|---|---|---|
| | | 1-H | 3-H | 5-H | 6-H | 7-H |
| VII | $CCl_4$ | 6,83 bs | 6,98 qn | 7,80 dt | 6,25 t | 7,39 qr |
| VIII | $CDCl_3$ | —b | —b | 8,01 dt | 6,48 t | —b |
| IX | $CDCl_3$ | 7,37 qr[c] | —b | 8,00 dt | 6,47 t | —b |
| | $CF_3COOH$ | 8,15 bs | 5,98 (2H) | 9,06 d | 7,77 t | 9,06 d |
| XI | $CDCl_3$ | 7,35 qr[c] | —b | 7,97 dt | 6,48 t | 7,55 qr |
| XIIa | $CDCl_3$ | 7,08 bs | 2,57 s | 10,18 dt | 6,80 t | 7,91 qr |
| | $CF_3COOH$ | 7,68 bs | 2,93 s | 9,97 dt | 7,57 t | 8,71 qr |
| XIIIa | $CCl_4$ | 7,15 d | 1,98 | 10,14 dt | 6,82 t | 7,86 qr |
| XIId | $CDCl_3$ | 7,25 bs | — | 10,47 dt | 7,15 t | 8,25 qr |
| | $CF_3COOH$ | 7,95 bs | — | 10,20 dt | 7,95 t | 9,10 qr |
| XIIIc | $CDCl_3$ | 7,68 d | — | 10,50 dt | 7,13 t | 8,30 qr |
| XIIc | $CDCl_3$ | 7,05 bs | 7,20—7,85 | 9,85 dt | 6,81 t | 7,97 qr |
| XVIa | $CDCl_3$ | —b | 7,20—7,91 | 9,86 dt | 6,95 t | 7,95 qr |
| XVId | $CDCl_3$ | 7,01 d | 3,87 (2H) s<br>2,33 (4H) m<br>3,57 (4H) m | 8,46 dt | 6,62 t | —b |
| XVe | $CDCl_3$ | 2,16 (4H) m<br>3,48 (4H) m<br>3,65 (2H) s | 2,16 (4H) m<br>3,48 (4H) m<br>3,85 (2H) s | 8,33 dt | 6,53 t | —b |

*a) Abbreviations: s is singlet, bs is broad signal, d is doublet, t is triplet, qr is quartet, dt is doublet of triplets, qn is quintet, and m is multiplet. b) The signals are found in the region of the protons of the phenyl residue. c) $J_{15}$ = 0.9 Hz, and $J_{13}$ ~ 12 Hz.

The protonation of 2-(p-tolyl)-8-carbethoxyindolizine (IX) and 2-methyl-3-acetyl(nitroso)-8-carbethoxyindolizines (XIIa and XIId) was studied. A comparison of the PMR spectra of the neutral IX molecule (in $CDCl_3$) and the cation (in $CF_3COOH$) demonstrates unambiguously that the cation of IX has a structure corresponding to the addition of a proton to the $C_{(3)}$ atom. On passing from the neutral molecule to the cation the signals of all of the aromatic protons are shifted 1.1-1.5 ppm to the weaker-field region, the 1-H proton is shifted 0.78 ppm to the weaker-field region, and a signal with an intensity of two proton units appears at 5.28 ppm; the latter was assigned to the protons of the methylene group in the 3 position.




The presence of NO and $COCH_3$ substituents in the 3 position changes the protonation center. As seen from Table 2, the signal of the proton in the 5 position is shifted to the strong-field region ($\Delta\delta$ = 0.21-0.27 ppm) on passing from the neutral molecule to the cation, while the signals of the remaining protons are shifted 0.6-0.8 ppm to the weak-field region. The complete analogy between the spectra of the conjugate acids of 3-acyl- and 3-nitroso-8-carbethoxyindolizines (XIIa and XIId) and the corresponding 3-acetyl- and 3-nitroso-6(7)-carbethoxyindolizines constitutes evidence for protonation of XIIa and XIId at the oxygen atom of the substituent.

Quantitative estimates of the basicities of 2-methyl(aryl)-8-carbethoxyindolizines and their derivatives were made by means of potentiometric titration. The differences in the pH values at the half-neutralization points of nitromethane solutions of diphenylguanidine and the investigated compounds were determined. The $\Delta pK_a$ values found are a measure of the basicities of the compounds: VII 7.40, VIII 8.85, IX 8.30, X 7.95, XI 10.42, XIIa and XIIb > 11, XIId 6.10, XIIIa > 11, XIIIc 6.82, XIVa > 11, XIVc 6.65, XVd 6.65, and XVIb 7.45.

The $\Delta pK_a$ values in the 2-aryl-8-carbethoxyindolizine series correlate satisfactorily with the Hammett $\sigma_p$ constants for substituents in the para position of the phenyl ring:

$$\Delta pK_a = 8.686 + 2.283\sigma_p \quad (r\ 0.994;\ s^2\ 0.03)$$

A similar correlation is also observed in the 2-aryl-3-nitroso-8-carbethoxyindolizine series: In connection with the exocyclic orientation of the protonation center, the δ coef-

ficient is small: $\Delta pK_a$ = 6.825 + 0.797 (r 0.996 and $s^2$ 0.001). The $\Delta pK_a$ value changes by several orders of magnitude on passing from $C_{(3)}$-unsubstituted 8-carbethoxyindolizines to 3-formyl-, 3-acetyl-, and 3-nitro derivatives; this is explained by a change in the protonation center and is in good agreement with the PMR spectral data.

It should be noted that the basicities of 2-methyl(aryl)-8-carbethoxyindolizines and their 3-substituted derivatives are close to the analogous characteristics of 6-carbethoxyindolizine compounds but differ substantially from those of 7-carbethoxyindolizine derivatives [1]. These data are in quite satsifactory agreement with the experimentally observed differences in the reactivities of the indicated three series of carbethoxyindolizines with respect to electrophilic reagents.

## EXPERIMENTAL

The PMR spectra of the neutral forms (in $CCl_4$ and $CDCl_3$) and protonated forms (in $CF_3COOH$) of the indolizines were recorded with a JEOL C-60 spectrometer (60 MHz) with tetramethylsilane as the internal standard. Potentiometric titration was carried out with a Radiometer automatic apparatus (Denmark) with a glass–calomel electrode couple at 30°C in nitromethane. A 0.5 N solution of perchloric acid in nitromethane was used as the titrant. The concentration of the unprotonated base at the half-neutralization point was ~0.008 mole/liter. Diphenylguanidine was used as the standard in the determination of the $\Delta pK_a$ values.

1-Phenyl-2-methyl-3-carbethoxypyridinium Bromide (III). A solution of 4 g (24 mmole) of 2-methyl-3-carbethoxypyridine (I) and 5.2 g (24 mmole) of phenacyl bromide was refluxed for 7 h, after which the mixture was cooled, and the resulting precipitate was removed by filtration and washed with ether to give 7.4 g (81%) of a product with mp 157-158°C (from methanol). Found: C 56.0; H 4.8; Br 21.6%. $C_{17}H_{18}BrNO_3$. Calculated: C 56.0; H 4.9; Br 21.9%.

1-(p-Nitrophenacyl)-2-methyl-3-carbethocypyridinium Bromide (VI). This compound, with mp 110-112°C (from methanol), was similarly obtained in 87% yield. Found: C 49.9; H 4.2; Br 19.7%. $C_{17}H_{17}BrN_2O_5$. Calculated: C 49.9; H 4.2; Br 19.5%.

2-Methyl-8-carbethoxyindolizine (VII). A solution of 10.4 g (63.2 mmole) of I and 8.7 g (64 mmole) of bromoacetone in 20 ml of acetone was refluxed for 7 h, after which the acetone was removed by vacuum distillition, and the residual oil was triturated with ether. The ether was decanted, and the residue was dissolved in 200 ml of absolute ethanol. Dry sodium bicarbonate [8.2 g (98 mmole)] was added to the solution, and the mixture was refluxed with vigorous stirring for 2 h. It was then vacuum evaporated, and 100 ml of water was added to the residue. The mixture was extracted with ether, and the extract was worked up to give 8.1 g (68%) of indolizine VII with bp 115-116°C (0.4 mm) [5].

2-Phenyl-8-carbethoxyindolizine (VIII). A total of 15 ml of 25% ammonium hydroxide was added with ice cooling to a solution of 7.2 g (20 mmole) of III in 50 ml of water, and after 30 min the bright-orange precipitate of the anhydro base was removed by filtration and recrystallized from isopropyl alcohol to give 2.9 g (55%) of indolizine VIII in the form of a light-yellow crystalline powder with mp 83-85°C (from ether). Found: C 76.7; H 5.6; N 5.2%. $C_{17}H_{15}NO_2$. Calculated: C 76.9; H 5.6; N 5.2%. The following compounds were similarly obtained but without isolation of the quaternary salts.

2-(p-Tolyl)-8-carbethoxyindolizine (IX). This compound, with mp 98-100°C (from isopropyl alcohol), was obtained in 61% yield. Found: C 77.0; H 6.0%. $C_{18}H_{17}NO_2$. Calculated: C 77.4; H 6.1%.

2-(p-Methoxyphenyl)-8-carbethoxyindolizine (X). This compound, with mp 170-172°C (from isopropyl alcohol), was obtained in 85% yield. Found: C 73.5; H 5.8; N 4.7%. $C_{18}H_{17}NO_3$. Calculated: C 73.2; H 5.8; N 4.7%.

2-(p-Nitrophenyl)-8-carbethoxyindolizine (XI). This compound, with mp 177-179°C (from isopropyl alcohol), was obtained in 80% yield. Found: C 66.1; H 4.8; N 9.1%: $C_{17}H_{14}N_2O_4$. Calculated: C 66.0; H 4.6; N 9.0%.

2-Phenylindolizine-8-carboxylic Acid Hydrazide. A mixture of 1.3 g (5 mmole) of VIII and 20 ml of hydrazine hydrate was refluxed for 4 h, after which the precipitate was removed by filtration and washed thoroughly with water to give 1.06 g (85%) of a product with mp 165-167°C (from ethanol). Found: C 71.8; H 5.2; N 16.7%. $C_{15}H_{13}N_3O$. Calculated: C 71.7; H 5.2; N 16.7%.

The following hydrazides were similarly obtained.

2-(p-Tolyl)indolizine-8-carboxylic Acid Hydrazide. This compound, with mp 170-172°C (from ethanol), was obtained in 84% yield. Found: C 72.5; H 5.6; N 15.4%. $C_{15}H_{15}N_3O$. Calculated: C 72.4; H 5.5; N 15.7%.

2-(p-Methoxyphenyl)indolizine-8-carboxylic Acid Hydrazide. This compound, with mp 130-132°C (from DMF), was obtained in 98% yield. The reaction time was 7 h. Found: C 67.9; H 5.7; N 14.9%. $C_{16}H_{15}N_3O_2$. Calculated: C 68.3; H 5.5; N 14.9%.

(2-Phenyl-8-indolizinyl)diphenylmethanol. An ether solution of 1 g (3.8 mmole) of VIII was added at −3 to −5°C to an ether solution of phenyllithium, obtained from 2.36 g (15 mmole) of bromobenzene and 0.21 g (0.3 mole) of lithium in 20 ml of ether, after which the mixture was allowed to stand at room temperature for 16 h and refluxed for 3 h. It was then cooled to 0°C and treated with 10 ml of water, and the aqueous mixture was extracted with ether. The ether extract was dried with magnesium sulfate and evaporated, and the residue was recrystallized twice from benzene to give 0.3 g (31%) of a product with mp 175-177°C. Found: C 86.6; H 5.7; N 3.5%. $C_{27}H_{21}NO$. Calculated: C 86.4; H 5.6; N 3.7%.

Electrophilic Substitution Reactions. Method A. A solution of 5 mmole of the indolizine derivative in 10 ml of acetic anhydride was heated at 100°C for 10 h (in the case of VII-IX) or refluxed for 14 h (in the case of X), after which the mixture was cooled and poured into ice water, and the precipitate was removed by filtration and recrystallized.

Method B. A 1.47-g (9.6 mmole) sample of phosphorus oxychloride was added gradually at 0°C to 2.5 ml of DMF, after which the mixture was allowed to stand at room temperature for 15 min. It was then cooled to 0°C, and a solution of 4.8 mmole of indolizine VII or X in 10 ml of DMF was added. The mixture was stirred at 0°C for another 2 h, after which it was poured over ice, and the aqueous mixture was neutralized with 50% potassium carbonate solution. The resulting precipitate was removed by filtration and washed with water.

Method C. A solution of 2 mmole of indolizine VII-XI in 2 ml of benzoyl chloride was allowed to stand at room temperature for 2 h, after which it was poured into 20 ml of water, and the aqueous mixture was allowed to stand at 4°C for 20 h. The resulting precipitate was removed by filtration, washed with water, and recrystallized.

Method D. A 2-ml sample of a 20% solution of hydrogen chloride in alcohol was added with ice cooling to a solution of 3.5 mmole of indolizine VII-XI in 10 ml of DMF, after which 6 mmole of isoamyl nitrite was added, and the mixture was maintained at 20°C for 1 h. It was then poured into water, and the aqueous mixture was made alkaline with 50% potassium carbonate solution. The resulting precipitate was removed by filtration.

Method E. A solution of 3.5 mmole of indolizine VIII, IX, or XI and 14 mmole of bis-(dimethylamino)methane in 20 ml of dioxane was refluxed for 8-10 h, after which it was subjected to vacuum evaporation. In the case of XI the residue was recrystallized from a mixture of isopropyl alcohol and petroleum ether. In the case of VIII and IX the residue was dissolved in ether, and a solution of 3.5 mmole of tartaric acid in ethanol was added to the ether solution.

Method F. Dimethylformamide (20 ml) was added to a mixture of 15 mmole of 40% formalin and 15 mmole of morpholine, and the mixture was stirred for 30 min. A 3-mmole sample of indolizine IX-XI was then added, and stirring was continued for 3 h. The mixture was allowed to stand at 20°C for 20 h (in the case of X and XI) or 72 h (in the case of IX), after which it was poured into water, and the resulting precipitate was removed by filtration. In the case of IX the aqueous solution was made alkaline with potassium carbonate and extracted with benzene. The benzene was removed by distillation, the residue was dissolved in ether, and the ether solution was treated with an alcohol solution of tartaric acid.

The preparative method, the reaction times, the yields, the melting points, and the results of elementary analysis of XII-XVI are presented in Table 1.

## LITERATURE CITED


1. L. M. Alekseeva, G. G. Dvoryantseva, M. S. Goizman, T. S. Loseva, A. D. Yanina, E. E. Mikhlina, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 11, 1540 (1976).
2. E. E. Mikhlina, A. D. Yanina, G. S. Loseva, K. F. Turchin, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 7, 977 (1974).

3. T. S. Loseva, A. D. Yanina, E. E. Mikhlina, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 2, 209 (1976).
4. T. S. Loseva, A. D. Yanina, E. E. Mikhlina, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 3, 348 (1976).
5. I. Dainis, Austral. J. Chem., 25, 1003 (1972).

# AMINATION OF 5-AZACINNOLINE WITH AROMATIC AMINES

M. F. Budyka, P. B. Terent'ev, and A. N. Kost

UDC 547.852.9:542.958.3

The 5-azacinnoline molecule was subjected to quantum-mechanical calculation by the Hückel method. The formation of 4-amino derivatives in the case of the reaction of 5-azacinnoline with aliphatic amines in the presence of an oxidizing agent and of 4,4'-bis(5-azacinnolinyl) in the case of dimerization in an oxygen-free medium was substantiated theoretically. The possibility of reactions with anions of aromatic amines was predicted by means of the Klopman method. It is shown that, in practice, the reaction is actually accelerated and that, in conformity with theory, the reaction center is the nitrogen atom of the aromatic amine. Possible products involving reaction with the participation of the p-carbon atom of the arylamine were not recorded. As in the case of aliphatic amines, the formation of a dimer was observed in an oxygen-free medium. The structures of the compounds obtained were proved by means of a combination of physicochemical methods.

We have recently shown [1] that 5-azacinnoline (I) reacts smoothly without catalysts with aliphatic amines (at 18-20°C for several days) to give the corresponding 4-amino-5-azacinnolines. However, aromatic amines did not undergo reaction under these conditions.

According to the concepts developed by Klopman [2], the reactivities of two compounds, one of which is a donor and the other an acceptor, are determined by the relative difference in the energies of the lower vacant molecular orbital (LVMO, $E_{m+1}$) of the acceptor and the upper occupied molecular orbital (UOMO, $E_n$) of the donor. If ($E_{m+1} - E_n$) is large and ($E_n - E^*_{n-1}$) is small, the energy of the interaction between the boundary orbitals is insignificant, and the reaction is controlled by the distribution of charges in the molecules of the reagents. However, if ($E_{m+1} - E_n$) is small and ($E_n - E_{n-1}$) is large (degeneration of the boundary orbitals), the reaction is controlled by the distribution of the electron density on the boundary orbitals. The interaction (perturbation) energy can be estimated as $E = 2c_{i,m+1}c_{j,n}$, where $c_{i,m+1}$ and $c_{j,n}$ are the coefficients of the atomic orbitals (AO), respectively, for the LVMO of the acceptor and the UOMO of the donor. The strongest interaction will be observed between the atom (i) of the acceptor and that atom (j) of the donor for which these coefficients are maximal. If the molecule of one of the reagents (for example, the donor) contains only one reaction center (j is invariant), the reaction is controlled by the coefficients for the other reagent ($c_{i,m+1}$ of the acceptor).

Using the simple Hückel method [3] and the parameters in [3, 4] ($h_N = 0.5$, $h_{N'} = 0.55$, $h_{C'} = 0.1$, $K_{CN} = 0.8$, and $K_{NN} = 0.6$) we calculated the electron density distribution on the atoms in the 5-azacinnoline molecule and the $c_{i,m+1}$ coefficients for the LVMO (Table 1). The maximum positive $\pi$ charge is observed for the carbon atom in the 6 position, and the maximum value of the $c_{i,m+1}$ coefficient from the carbon atoms is observed for the carbon atom in the 4 position. The coulombic interaction is small in the case of the reaction with aliphatic amines, the reaction is controlled by the boundary electron density, and the ring 4-C atom should be the most reactive atom. In fact, the formation of products of nucleophilic substitution of the 4-H atom by aliphatic amines has been observed [1].

*The symbol $E_{n-1}$ indicates the energy of the occupied orbital of the donor closest to $E_n$.

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 809-812, June, 1978. Original article submitted July 11, 1977.

0009-3122/78/1406-0663$07.50  