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# HETARYLATION OF INDOLIZINES

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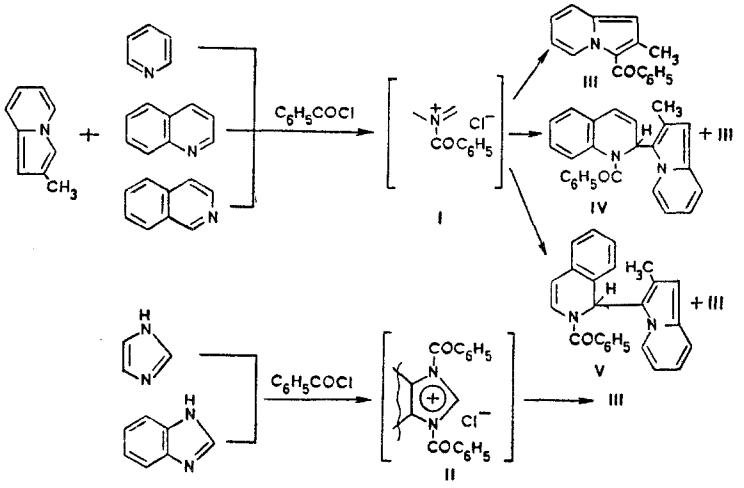
UDC 547.758.7'759.2'785.5'833'835

The direct incorporation of quinoline, isoquinoline, acridine, imidazole, and benzimidazole residues in the indolizine ring was accomplished by reaction of N-heteroaromatic compounds with indolizine derivatives in the presence of acylating agents.

Indolizine readily undergoes electrophilic substitution reactions, during which the 1 and 3 positions, the relative reactivities of which in these reactions are determined by the 1 : 3 isomer ratio, undergo electrophilic attack [1].

We have found that 2-methylindolizine may undergo both hetarylation [2] and acylation on reaction with N-heteroaromatic systems in the presence of acyl halides. Heterocyclic derivatives of the IV and V type are formed in the hetarylation of 2-methylindolizine, whereas 2-methyl-3-acylindolizines III are obtained in the case of acylation:



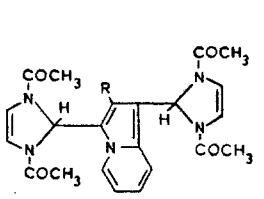
The relative amounts of acylation and hetarylation products depend on many factors but mainly on the nature of the N-heteroaromatic cation.

Thus only acylation of the indolizine ring with the quantitative formation of III occurs when N-acyl pyridinium salts I in situ and N,N'-diacylimidazolium and benzimidazolium chlorides II are used. The more stable N-acyl quinolinium and isoquinolinium cations form both types of reaction products, during which the formation of 2-methyl-3-acylindolizine III proceeds to a greater extent with quinoline than with isoquinoline. Characteristic $\nu_{C=O}$ bands at 1660-1680 $cm^{-1}$ and $\nu_{C=C}$ bands at 1610-1620 $cm^{-1}$ are observed in the IR spectra of hetarylation products IV and V; this, taken together with the set of mass spectrometric data – the presence in the spectra of a molecular ion, $C_6H_5CO$ fragments, and fragments of quinoline, isoquinoline, and indolizine residues – confirms their structure [3].

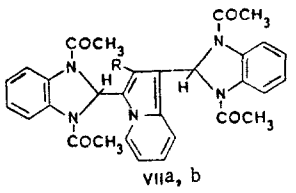
Dnepropetrovsk Engineering-Construction Institute, Dnepropetrovsk 320000. Donetsk State University, Donetsk 340055. Scientific-Research Institute of Rubber and Latex Articles, Moscow 107061. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1510-1514, November, 1977. Original article submitted October 25, 1976.

We were able to realize the incorporation of imidazole and benzimidazole residues in the indolizine ring by using acetic anhydride as the acylating agent. In this case only products of bishetarylation of indolizine (VI and VII) were obtained:



VIa, b

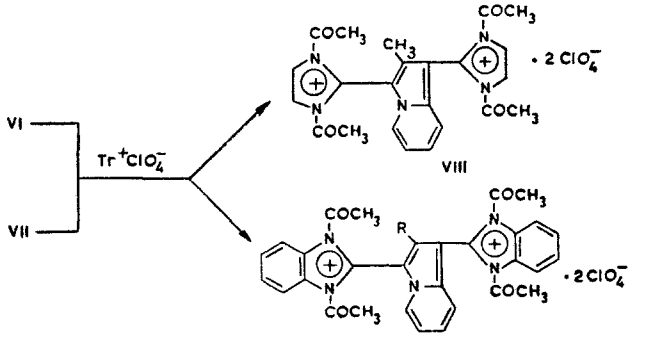


VIIa, b

VI, VII a $R=CH_3$, b $R=C_6H_5$

Fragmentation of the molecular ion ($M^+$) due to cleavage of the $\sigma$ bond between the hetaryl rings is observed in the mass spectrum of VIIa. The elementary compositions of $M^+$ and the principal fragment ions determined by means of high-resolution mass spectra are presented in Table 1.

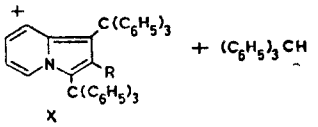
Compounds VI and VII react with triphenylmethyl perchlorate to give stable N,N'-diacyl salts VIII and IX and, as a side product, 1,3-bis(triphenylmethyl)indolizine (X), evidently as a result of partial decomposition of the starting compounds:



VIII



IXa, b

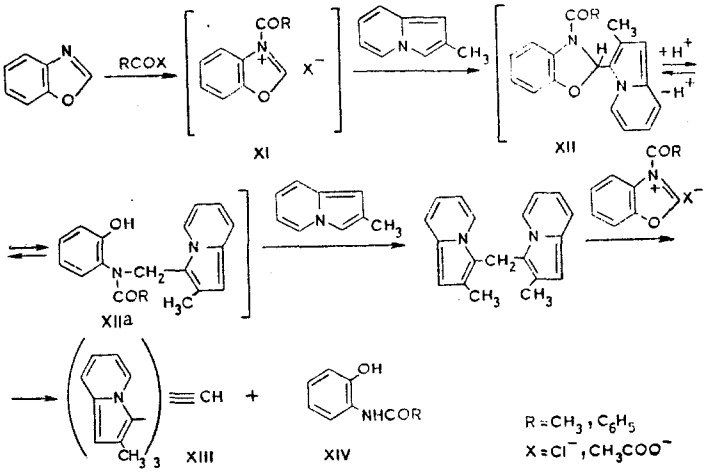


X

IX a $R=CH_3$, b $R=C_6H_5$

The structure of X was proved by its synthesis by an independent method.

Benzoxazole behaves anomalously in its reaction with indolizine under similar conditions. In the presence of various acylating agents we obtained the same compound, to which we assigned the tri(3-indolizyl)methane structure (XIII). Intermediate salt XI evidently attacks the indolizine ring to give XII, which is in dynamic equilibrium with open form XIIa; the latter is unstable and is converted to XIII:



XI

XII

XIIa

XIII

XIV

$R=CH_3, C_6H_5$

$X=Cl^-, CH_3COO^-$

TABLE 1. Elementary Compositions of the Ions Formed in the Fragmentation of VIIa (M/ΔM = 12,000)

| Empirical composition of the ions | Precise determination of the mass | | Fragmentation of $M^+$ |
|---|---|---|---|
| | calc. | exptl. | |
| $C_{31}H_{29}N_5O_4$ | 535,22206 | 535,22220 | $M^{+\cdot}$ |
| $C_{20}H_{19}N_3O_2$ | 333,14780 | 333,14800 | $[M-C_{11}H_{10}N_2O_2]^{+\cdot}$ (A) |
| $C_{18}H_{17}N_3O$ | 291,13723 | 291,13760 | $[A-C_2H_2O]^{+\cdot}$ |
| $C_{16}H_{14}N_3$ | 248,11883 | 248,11900 | $[A-C_2H_2O, -C_2H_3O]^+$ |
| $C_{11}H_{12}N_2O_2$ | 204,08990 | 204,09000 | $[A-C_9H_7N]^{+\cdot}$ (B) |
| $C_7H_7N_2$ | 119,06095 | 119,06100 | $[B-CH_2CO, -C_2H_3O]^+$ |

TABLE 2. Heterocyclic Derivatives of Indolizine

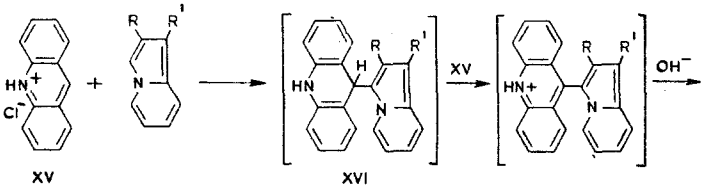
| Compound | mp, °C[a] | $R_f$[b] | Found, % | | | Empirical formula | Calc., % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | | C | H | N | |
| VIIb | 275—276 | 0,3 | 72,5 | 5,4 | 11,8 | $C_{36}H_{13}N_5O_4$ | 72,5 | 5,2 | 11,6 | 30 |
| XVIIb | 266—266,5 | 0,5 | 87,6 | 5,0 | 7,0 | $C_{29}H_{20}N_2O$ | 87,9 | 5,1 | 7,1 | 30 |
| XVIIc | 265—266 | 0,6 | 89,2 | 5,0 | 5,9 | $C_{34}H_{22}N_2O$ | 89,1 | 4,8 | 6,1 | 87 |
| XVIII[a] | 266—267 | 0,5 | 85,6 | 5,3 | 9,2 | $C_{22}H_{16}N_2$ | 85,7 | 5,2 | 9,1 | 81 |
| XVIII[b] | >300 | 0,4 | 86,4 | 5,0 | 7,5 | $C_{27}H_{18}N_2$ | 86,5 | 4,9 | 7,6 | 52 |

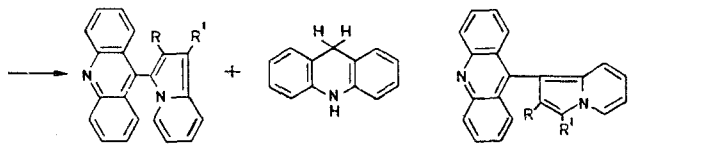
[a]From DMF. [b]In system B.

Evidence for the correctness of the proposed scheme is provided by the fact that N-acyl-o-aminophenol XIV was isolated as a side product. This type of transformation of N,N'-diacylbenzimidazolium salts has also been previously observed in some cases [4].

The high-resolution mass spectrum of XIII confirms its elementary composition (the experimentally determined mass number for the empirical formula $C_{28}H_{25}N_3$ is 403.2042, as compared with the calculated value of 403.20496).

It was found to be more convenient to use protic acridinium salts rather than N-acyl acridinium salts for the introduction of an acridine residue into the indolizine ring. The reaction in this case evidently proceeds with hydride-ion transfer from the intermediately formed dihydro derivatives XVI to salt XV, as has been shown in the case of hetarylation of dialkylanilines and indoles [5]:




XVII a R=CH$_3$, R'=CH$_3$, b R=CH$_3$, R'=COC$_6$H$_5$, c R=C$_6$H$_5$, R'=COC$_6$H$_5$

XVIII a R=CH$_3$, R'=H, b R=C$_6$H$_5$, R'=H

The UV and IR spectra of all XVII and XVIII are similar to the spectra of 1-(9-acridinyl)-2,3-dimethylindolizine (XVIIa), the structure of which was proved by mass spectrometry; this confirms the assigned structures for the acridinylindolizine derivatives obtained (XVII and XVIII). The IR spectra of XVII and XVIII do not contain absorption bands in the region of the NH group; this excludes the XVI dihydro derivative structure.

Thus we were able to develop methods for the direct introduction of quinoline, isoquinoline, acridine, imidazole, and benzimidazole residues into the indolizine ring.

## EXPERIMENTAL

The IR spectra of chloroform solutions of the compounds were recorded with a UR-20 spectrometer. The mass spectra were obtained with a Varian MAT-311 spectrometer under the following conditions: accelerating voltage 3 kV, cathode emission current 300 mA, ionizing voltage 70 eV, and ion source temperature 115-130 deg

C. Chromatography was carried out in a loose thin layer of aluminum oxide (active II in the Brockmann classification) with elution with chloroform–benzene–hexane (30 : 6 : 1) (system A) and chloroform–benzene–hexane–methanol (30 : 6 : 1 : 1) (system B) and development with iodine vapors and in UV light.

2-Methyl-3-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)indolizine (V). A mixture of 6.4 g (50 mmole) of isoquinoline, 3.2 g (25 mmole) of 2-methylindolizine, and 3.5 g (25 mmole) of benzoyl chloride in 35 ml of dry benzene was refluxed for 8 h, after which it was subjected to steam distillation. The residue in the distillation flask was separated and recrystallized from methanol to give 6 g (60%) of a product with mp 169-170 deg C and $R_f$ 0.4 (system A). IR spectrum: 1650 (C = O) and 1610 $cm^{-1}$ (C = C). Found: C 82.5; H 5.3; N 7.8%. $C_{25}H_{20}N_2O$. Calculated: C 82.6; H 5.2; N 7.7%. The mother liquor from the recrystallization was worked up to give 2 g (33%) of 2-methyl-3-benzoylindolizine III with mp 65-66 deg (from hexane) and $R_f$ 0.7 (system A). IR spectrum: 1710 $cm^{-1}$ (C = O). Found: C 81.5; H 5.7; N 5.9%. $C_{16}H_{13}NO$. Calculated: C 81.6; H 5.5; N 5.9%. According to the data in [6], III had mp 65-66 deg C.

2-Methyl-3-(1-benzoyl-1,2-dihydro-2-quinolinyl)indolizine (IV). This compound was similarly obtained by reaction of 6.4 g (50 mmole) of quinoline, 3.2 g (25 mmole) of 2-methylindolizine, and 3.5 g (25 mmole) of benzoyl chloride. Workup gave 3.3 g (33%) of a product with mp 139-140 deg C (from methanol) and $R_f$ 0.3 (system A). IR spectrum: 1665 (C = O) and 1612 $cm^{-1}$ (C = C). Found: 82.4; H 5.3; N 7.4%. $C_{25}H_{20}N_2O$. Calculated: C 82.6; H 5.2; N 7.7%. We also isolated 4 g (66%) of 2-methyl-3-benzoylindolizine III.

2-Methyl-1,3-bis(N,N'-diacetyl-2,3-dihydro-2-imidazolyl)indolizine (VIa). A mixture of 3.4 g (25 mmole) of imidazole and 3.2 g (25 mmole) of 2-methylindolizine in 15 ml of acetic anhydride was allowed to stand at 25 deg C for 4 h, after which the precipitate was separated and recrystallized from dimethylformamide (DMF) to give 4.8 g (55%) with mp 215-216 deg C and $R_f$ 0.2 (system A). IR spectrum: 1665 (C = C), 1620 (C = C), and 3150 $cm^{-1}$ (≥ C–H). Found: C 63.4; H 6.0; N 16.2%. $C_{23}H_{25}N_5O_4$. Calculated: C 63.5; H 5.9; N 16.1%.

2-Methyl-1,3-bis(N,N'-diacetyl-2,3-dihydro-2-benzimidazolyl)indolizine (VIIa). This compound, with mp 252-253 deg C (from DMF) and $R_f$ 0.6 (system B), was similarly obtained in 93% yield. IR spectrum: 1665 $cm^{-1}$ (C = O). Mass spectrum, m/e (%): 77 (18.8); 78 (8.5); 91 (14.4); 92 (6.5); 118 (11.6); 119 (19.1); 129 (100.0); 130 (15.0); 131 (8.4); 162 (5.7); 204 (10.7); 248 (13.0); 291 (15.4); 333 (9.5); 535 (2.3). Found: C 69.4; H 5.6; N 13.1%. $C_{31}H_{29}N_5O_4$. Calculated: C 69.5; H 5.4; N 13.1%. (See Table 2 for data on VIIb.)

Tris(2-methyl-3-indolizyl)methane (XIII). A mixture of 3.2 g (25 mmole) of 2-methylindolizine and 3.0 g (25 mmole) of benzoxazole in 15 ml of acetic anhydride was allowed to stand at room temperature for 3 h, after which the resulting precipitate was separated, washed with methanol, and recrystallized from DMF to give 2.0 g (14%) of a product with mp 171-172 deg C and $R_f$ 0.9 (system A). Mass spectrum, m/e (%): 77 (5.1); 78 (13.1); 92 (35.1); 130 (20.2); 131 (17.8); 143 (14.0); 144 (47.0); 256 (14.5); 257 (42.7); 258 (16.0); 271 (40.1); 272 (48.0); 273 (26.4); 295 (17.9); 296 (18.1); 310 (19.9); 311 (48.8); 312 (11.1); 388 (38.5); 389 (11.1); 402 (19.4); 403 (100.0); 404 (31.2). Found: C 82.7; H 6.4; N 10.5%. $C_{28}H_{25}N_3$. Calculated: C 83.0; H 6.4; N 10.5%. Workup of the filtrate gave 5 g (67%) of N-acetyl-o-aminophenol XIV with mp 121-122 deg C (from ethanol) and $R_f$ 0.2 (system A). No melting-point depression was observed for a mixture of this product with an authentic sample.

Reaction of 2-Phenyl-1,3-bis(N,N'-diacetyl-2,3-dihydro-2-benzimidazolyl)indolizine with Triphenylmethyl Perchlorate. A solution of 0.7 g (2 mmole) of triphenylmethyl perchlorate in 10 ml of dry acetonitrile was added to a solution of 0.6 g (1 mmole) of 2-phenyl-1,3-bis(N,N'-diacetyl-2,3-dihydro-2-benzimidazolyl)-indolizine (VIIb) in 10 ml of dry acetonitrile, and the mixture was allowed to stand at 25 deg C for 10 min. It was then poured into 150 ml of dry ether, and the resulting precipitate was removed by filtration and purified by reprecipitation from acetonitrile solution by the addition of ether to give 0.5 g (62%) of 2-phenyl-1,3-bis-(N,N'-diacetyl-2-benzimidazolia)indolizine diperchlorate (IXb) with mp 160-161 deg C (acetonitrile with ether). IR spectrum (in acetonitrile): 1745 $cm^{-1}$ (C = O). Found: C 50.1; H 4.0; N 8.5; Cl 9.0%. $C_{36}H_{27}N_5O_4 \cdot 2HClO_4$. Calculated: C 49.9; H 3.7; N 8.7; Cl 8.9%. The ether was removed from the filtrate by distillation, and the residue was washed with methanol and recrystallized from DMF to give 0.2 g (29%) of 1,3-bis(triphenylmethyl)-2-phenylindolizine (X) with mp 240-241 deg C and $R_f$ 0.7 (system A). Found: C 92.0; H 6.0; N 1.8%. $C_{52}H_{39}N$. Calculated: C 92.1; H 5.8; N 2.1%. A similar procedure was used to obtain 2-methyl-1,3-bis(N,N'-diacetyl-2-benzimidazolia)indolizine diperchlorate, with mp 184-185 deg C (acetonitrile with ether), in 68% yield. IR spectrum: 1750 $cm^{-1}$ (C = O). Found: C 50.6; H 3.9; N 9.2; Cl 9.3%. $C_{31}H_{25}N_5O_4 \cdot 2HClO_4$. Calculated: C 50.8; H 3.7; N 9.5; Cl 9.6%.

Reaction of 2-Phenylindolizine with Triphenylmethyl Perchlorate. A solution of 0.7 g (2 mmole) of triphenylmethyl perchlorate in 10 ml of dry acetonitrile was added to a solution of 0.2 g (1 mmole) of 2-phenyl-

indolizine in 10 ml of dry acetonitrile, and the mixture was allowed to stand at room temperature for 10 min. The acetonitrile was then removed by distillation, and the residue was washed with methanol and recrystallized from DMF to give 0.5 g (71%) of 1,3-bis(triphenylmethyl)-2-phenylindolizine with mp 240-241 deg C. The product did not depress the melting point of a sample of the compound described above.

2,3-Dimethyl-1-(9-acridinyl)indolizine (XVIIa). This compound was obtained by reaction of 10 g (50 mmole) of acridine hydrochloride and 5.8 g (25 mmole) of 2,3-dimethylindolizine in 35 ml of dry DMF at 100 deg C for 8 h. Workup gave 4.8 g (60%) of a product with mp 274-275 deg C (from DMF) and $R_f$ 0.6 (system B). Mass spectrum, m/e (system A): 152 (15.10); 152.5 (2.4); 153 (13.0); 153.5 (8.4); 158.5 (4.2); 159 (3.6); 159.5 (2.4); 160 (8.7); 160.5 (4.9); 161 (9.2); 304 (3.0); 305 (12.4); 306 (6.2); 307 (4.7); 318 (3.0); 319 (4.5); 320 (3.0); 321 (43.8); 322 (100.0); 323 (25.9). Found: C 85.9; H 5.7; N 8.6%. $C_{23}H_{18}N_2$. Calculated: C 85.7; H 5.6; N 8.7%. Compounds XVIIb, c and XVIIIa, b were similarly obtained (see Table 2).

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# REACTION OF α-CYANOMETHYLAZAHETEROCYCLES WITH α-HALO CARBOXYLIC ACID CHLORIDES AND ANHYDRIDES


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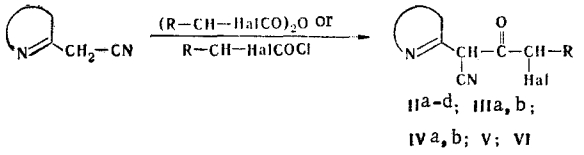
UDC 542.951:547.78'82



α-Cyanomethylazaheterocycles are acylated by α-halo carboxylic acid chlorides and anhydrides at the methylene carbon atom to give hetaryl-containing halo ketones.


α-Cyanomethylazaheterocycles (I) are acylated at the methylene carbon atom [1-3] to give α-acyl derivatives. However, up until now acyl derivatives that contain a functional group in the acyl residue have not been obtained. In the present research we obtained compounds of this type and studied their properties.




IIa-d; IIIa, b; IVa, b; V; VI

In the acylation of 2-cyanomethyl derivatives of azaheterocycles of the I type with α-halocarboxylic acid anhydrides and chlorides the reaction may proceed via three pathways: acylation and alkylation of the hetero-ring nitrogen atom or acylation of the methylene group. In all of the cases that we studied we isolated only C-acylated pyridines (IIa-d), quinolines (IIIa, b), benzimidazoles (IVa, b), 1-methylbenzimidazoles (V), and 4,5-diphenylthiazoles (VI) (see Table 1), the structures of which were confirmed by their chemical properties and spectral data. Three maxima at 240, 295, and 370 nm are observed in the UV spectra of acyl derivatives of 2-cyanomethylpyridine IIa, b, d in ethanol; this is in complete agreement with the data for α-acetyl-2-cyano-methylpyridine [3]. A singlet of protons of a methylene group at 4.5-4.8 ppm is observed in the PMR spectra of the haloacetyl derivatives (IIa, III, IVa, V, and VI). The absorption band in the IR spectra at 2195-2205 $cm^{-1}$ is related to a conjugated nitrile group [2, 3].

In the acylation of α-halo carboxylic acid chlorides half the amount of starting azaheterocycle is tied up in the form of the hydrochloride, and the yields of acyl derivatives do not even reach 50%. When the reaction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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1515-1517, November, 1977. Original article submitted November 15, 1976.