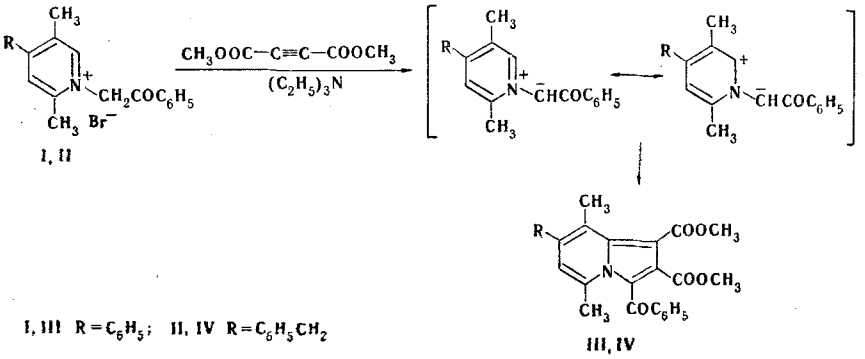
SUBSTITUTED INDOLIZINES AND INDENOINDOLIZINES

N. S. Prostakov, L. A. Gaivoronskaya,
Rogiros Anastasi, Kamara Maiha Sarata Mohomon,
and A. A. Savina

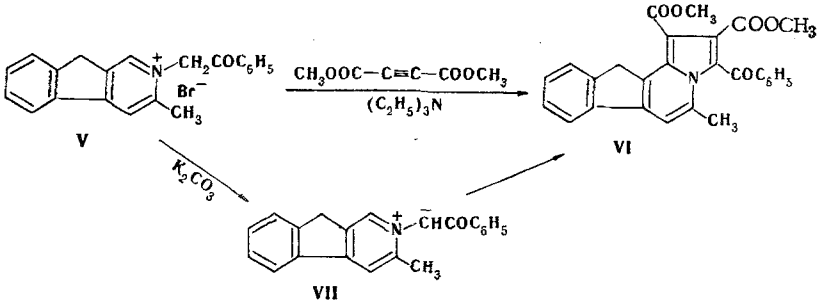
UDC 547.758.7'759

Indolizines, indeno[1,2-g]indolizine, and indeno[1,2-e]indolizine containing benzoyl and carbomethoxy groups in the five-membered ring were obtained, respectively, by condensation of ring-substituted N-phenacylpyridinium bromide and the analogous 3-methyl-2-azafluorenium bromide quaternary salts, as well as 4-azafluorenium bromide, with dimethyl acetylenedicarboxylate in the presence of triethylamine. A substituted indeno[2,3-f]indolizine was obtained from the analogous quaternary 9-oxo-3-methyl-2-azafluorenium quaternary salt by the Chichibabin method. 9-Oxo-3-methyl-2-azafluorenium dibenzoylmethylid and 5-oxo-2-phenyl-3-benzoylindeno[2,3-f]indolizine were also synthesized. Deuterium exchange in 9-oxo-3-methyl-2-phenacyl-2-azafluorenium bromide was studied by means of PMR spectroscopy, and information regarding the protonation of the substituted indeno[2,3-f]indolizines was obtained.

6-Methyl-7-(2,4,5-trimethylbenzyl)-2-phenylindolizine, which was described in [1], has displayed growth-regulating activity that, according to the preliminary data, increases the activity of indoleacetic acid. Continuing our research in the indolizine series, we turned to the preparation of substituted indolizines by 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate (DMAD) to pyridinium ylids, which are formed in the reaction of triethylamine with quaternary pyridinium salts. 5,8-Dimethyl-7-phenyl(III)[benzyl(IV)]-3-benzoyl-1,2-dicarbomethoxyindolizines, the structure of which was confirmed by analytical and spectral data, were synthesized from 2,5-dimethyl-4-phenyl(I)[benzyl(II)]-1-phenacylpyridinium bromides [2].



The method of 1,3-dipolar cycloaddition was used in the syntheses of new heterocyclic systems of the indenoindolizine type. 4-Methyl-3-benzoyl-1,2-dicarbomethoxyindeno[1,2-g]-

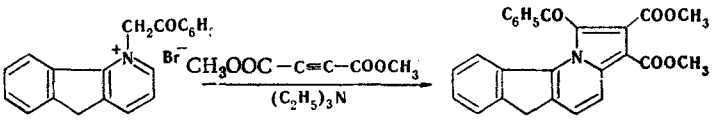


Patrice Lumumba International-Friendship University, Moscow 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 794-798, June, 1979. Original article submitted May 3, 1978.

0009-3122/79/1506-0647$07.50

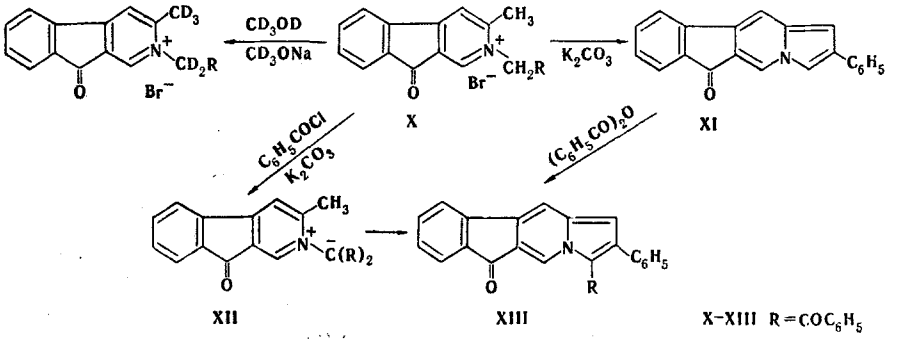
indolizine (VI) was obtained in the form of high-melting lemon-yellow crystals that are stable during storage by the reaction of 3-methyl-2-phenacyl-2-azafluorenium bromide (V) [3] with triethylamine and DMAD. The same indenoindolizine was isolated in very low yield in the case of a stepwise reaction — conversion of quaternary salt V to 3-methyl-2-azafluorenium benzoylmethylid (VII) and its subsequent reaction with DMAD.

The isomer of indenoindolizine VI with respect to the position of the nitrogen atom in the ring — 1-benzoyl-2,3-dicarbomethoxyindeno[1,2-e]indolizine (IX) — was synthesized from 4-phenacyl-4-azafluorenium bromide (VIII) and DMAD in the presence of triethylamine.



VIII IX

We used 9-oxo-3-methyl-2-phenacyl-2-azafluorenium bromide (X) as the starting compound for the synthesis of a compound with the indolizine structure by the Chichibabin method (conversion of quaternary α-alkyl-N-α-oxoalkylpyridinium salts to indolizines [4]). Information regarding the potential reaction centers of this compound under the conditions of the Chichibabin reaction was obtained during a study of the deuterium exchange of quaternary salt X in a 0.03 N solution of CD_3ONa in CD_3OD. The PMR spectra recorded 10 min after the addition of CD_3ONa do not contain signals of methylene protons of the phenacyl group, and the intensity of the signal of the α-CH_3 group decreases sharply (by 90%) vis-à-vis retention of the parameters of the remaining signals (Fig. 1).



X XI XII XIII X-XIII R = COC_6H_5

5-Oxo-2-phenylindeno[2,3-f]indolizine (XI) was obtained both under the conditions for the formation of an ylid and under the conditions for cyclization by the Chichibabin method from quaternary salt X. Compound XI, like indolizines VI and IX, has a relatively high melting point and is colored. The two-proton singlet at 6.30 ppm in the PMR spectrum of indolizine XI in CF_3COOH is due to the protons attached to C_3 as a result of protonation of this position of the indeno[2,3-f]indolizine system (Fig. 2). The protonation of C_3-unsubstituted indolizines proceeds similarly [5]. However, the absence of a one-proton singlet in the indicated region of the PMR spectrum of XI in CF_3COOD indicates reversibility of protonation at C_3, as a consequence of which the protons in this position undergo complete exchange by deuterons. This fact is evidently due to the effect of the C=O group, which decreases the electron density on C_3 and is a second competitive protonation center.

Treatment of quaternary salt X with benzoyl chloride in the presence of a solution carbonate gave 9-oxo-3-methyl-2-azafluorenium dibenzoylmethylid (XII), which is relatively easily converted to 5-oxo-2-phenyl-3-benzoylindeno[2,3-f]indolizine (XIII) on storage or during crystallization. A singlet signal of a CH_3 group at 2.90 ppm is observed in the PMR spectrum of XII in CF_3COOH 35 min after isolation of this ylid from the reaction mixture, but the ratio of the integral intensity of this signal and the signal of the aromatic protons (multiplet at 6.97-8.47 ppm) does not correspond to the structure of ylid XII (≈1:10 instead of 1:5). The increase in the integral intensity of the signals of the aromatic protons by a factor of greater than two constitutes evidence for admixed indolizine XIII. The latter was synthesized by direct benzoylation of indolizine XI by the method in [6]. Only signals of aromatic protons at 6.87-8.5 ppm are present in the PMR spectrum of indolizine XIII in CF_3COOH. The absence of the signal of a methylene group indicates the impossibility of protonation of the five-membered nitrogen-containing ring in indolizine XIII at C_1 when there are electron-acceptor substituents attached to C_2 and C_3.

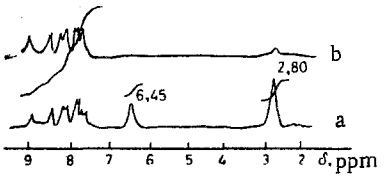


Fig. 1

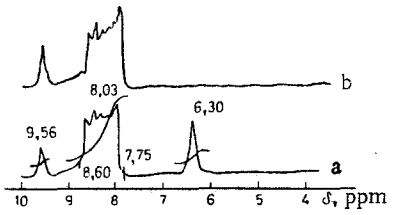


Fig. 2

Fig. 1. PMR spectrum of 9-oxo-3-methyl-2-phenacyl-2-azafluorenium bromide (X): a) in CD_3OD; b) in CD_3OD 10 min after the addition of a 0.03 N solution of CD_3ONa.

Fig. 2. PMR spectrum of 5-oxo-2-phenylindeno[2,3-f]-indolizine (XI): a) in CF_3COOH; b) in CF_3COOD.

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol (in chloroform in the case of VI) were measured with a Hitachi EPS-3T spectrophotometer. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Tesla BS-487C spectrometer (with a Jeol spectrometer in the case of VI). The mass spectra were obtained with an MKh-1303 spectrometer.

5,8-Dimethyl-7-phenyl-3-benzoyl-1,2-dicarbomethoxyindolizine (III). A 1.9-g (13.4 mmole) sample of DMAD and 1.4 g (14 mmole) of triethylamine were added at room temperature to a suspension of 2.5 g (6.5 mmole) of salt I (mp 209.5-210.5°C) in 20 ml of $CHCl_3$, and the mixture was refluxed for 6 h. The chloroform solution was cooled, washed with water, dried with magnesium sulfate, and evaporated. The residue was chromatographed with a column (activity II Al_2O_3 (200 g), 40 by 3 cm, elution with benzene) to give 0.32 g (11%) of bright-yellow crystals of indolizine III with mp 147-148°C (from ligroin). IR spectrum: 1728 and 1712 (two $COOCH_3$); 1668 cm^{-1} (diaryl ketone CO). UV spectrum, λ_{max} (log ε): 204 (4.62), 254 (4.86), 334 (4.10), 370 nm (3.80). PMR spectrum [$CDCl_3$, tetramethylsilane (TMS)], δ: 8.02 (q, 2H, o-H relative to CO), 7.32-7.62 (m, 8H, aromatic), 6.75 (s, 1H, 6-H), 4.05 and 3.67 (s, 3H each, $COOCH_3$), and 2.56 and 2.45 ppm (s, 3H each, CH_3). Found: C 73.1; H 5.5; N 3.3%; M^+ 441. $C_{27}H_{23}NO_5$. Calculated: C 73.4; H 5.4; N 3.2%; M 441.

5,8-Dimethyl-7-benzyl-3-benzoyl-1,2-dicarbomethoxyindolizine (IV). As in the synthesis of indolizine III, the reaction of 2.3 g (5.8 mmole) of salt II (mp 216-216.5°C) [2], 1.7 g (12 mmole) of DMAD, and 1.3 g (13 mmole) of triethylamine in 20 ml of $CHCl_3$ gave 0.31 g (12%) of bright-yellow crystals of indolizine IV with mp 149-151°C (from methanol). IR spectrum: 1732 and 1720 (two $COOCH_3$); 1670 cm^{-1} (diaryl ketone CO). UV spectrum, λ_{max} (log ε): 208 (5.00), 235 (5.14), 326 (4.28), 384 nm (4.20). PMR spectrum ($CDCl_3$, hexamethyldisiloxane), δ: 7.82 (q, 2H, o-H relative to CO), 7.00-7.52 (m, 8H, aromatic), 6.87 (s, 1H, 6-H), 3.95 (s, 2H, CH_2), 3.85 and 3.30 (s, 3H each, $COOCH_3$), and 2.40 and 2.20 ppm (s, 3H each, CH_3). Found: C 74.1; H 5.3; N 3.2%; M^+ 455. $C_{28}H_{25}NO_5$. Calculated: C 73.8; H 5.4; N 3.1%; M 455.

4-Methyl-3-benzoyl-1,2-dicarbomethoxyindeno[1,2-g]indolizine (VI). A) A mixture of 0.7 g (1.6 mmole) of salt V (mp 225-226.5°C) [3], 0.48 g (3.4 mmole) of DMAD, 0.4 g (4 mmole) of triethylamine, and 15 ml of methylene chloride was refluxed for 5 h with constant stirring, after which it was washed with water and dried with magnesium sulfate. The solvent was removed by distillation, and the residue was refluxed in 10 ml of methanol and filtered hot. The methanol-insoluble residue [0.14 g (17.5%)] was crystallized from acetonitrile to give indenoindolizine VI as lemon-yellow crystals with mp 231-232°C. IR spectrum: 1715 and inflection at 1723 (two $COOCH_3$); 1631 cm^{-1} (diaryl ketone CO). UV spectrum (in chloroform), λ_{max} (log ε): 266 (4.93), 290-300 shoulder (4.20), 360-380 shoulder (4.53), 400 nm (4.54). PMR spectrum ($CDCl_3$, TMS), δ: 7.86 (broad d, 2H, o-H relative to CO), 7.00-7.60 (m, 10H, aromatic), 4.32 (s, 2H, CH_2), 3.78 and 3.24 (s, 3H each, $COOCH_3$), and 2.40 ppm (s, 3H, CH_3). Found: C 73.8; H 4.6; N 3.3%; M^+ 439. $C_{27}H_{21}NO_5$. Calculated: C 74.0; H 4.8; N 3.3%; M 439.

B) A 1-g (2.6 mmole) sample of salt V and 3 ml of a 40% solution of potassium carbonate were shaken in 4 ml of water for 10 min, and the resulting orange-brown crystals were extracted with chloroform. The solution was filtered through a layer of Al_2O_3 (3 by 3 cm), after which the solvent was removed by distillation. The residue was triturated under abso-

lute ether, and the solid material was removed by filtration to give 0.65 g (88%) of ylid VII as a brown powder that decomposed at 130-140°C. A 0.5-g (3.5 mmole) of DMAD was added to a solution of 0.6 g (2.0 mmole) of ylid VII in 20 ml of acetonitrile, and the mixture was allowed to stand at room temperature for 2 days. The residue after removal of the solvent by distillation was chromatographed with a column [activity II Al_2O_3 (100 g), 40 by 2 cm, elution with ethyl acetate—heptane (1:6)]. Workup of the first portions of the elute yielded 0.02 g (2%) of indenoindolizine VI, which was identical to a sample obtained in experiment A with respect to its melting point and chromatographic mobility.

1-Benzoyl-2,3-dicarbomethoxyindeno[1,2-e]indolizine (IX). A) Quarternary salt VIII was obtained from equimolar amounts of 4-azafluorene [7] and bromoacetophenone in acetone by refluxing the mixture for 2 h (the product was obtained in 70% yield); the light-lilac-colored crystals had mp 220-221°C (from alcohol). IR spectrum: 1695 cm^{-1} (CO). PMR spectrum (CF_3COOH, TMS), δ: 8.65 (broad d, 2H, 3-H and 1-H or 5-H), 8.25 (broad d, 2H, o-H relative to CO), 7.25-8.00 (m, 8H, aromatic), 6.81 (s, 2H, N^+-CH_2), and 4.35 ppm (s, 2H, 9-CH_2). Found: Br 21.7; N 3.7%; (M^+—HBr) 285. $C_{20}H_{16}BrNO$. Calculated: Br 21.8; N 3.8%; M 366; (M—HBr) 285.

B) A mixture of 1 g (2.7 mmole) of salt VIII, 0.78 g (5.5 mmole) of DMAD, 0.62 g (6 mmole) of triethylamine, and 20 ml of chloroform was refluxed for 5 h, after which it was worked up as in the synthesis of indolizine III. The chromatographic column [activity II Al_2O_3 (100 g), 40 by 2 cm] was eluted successively with heptane and ether. Workup of the ether eluate gave 0.11 g (9.7%) of light-orange crystals of indenoindolizine IX with mp 210-210.5°C (from methanol). IR spectrum: 1740 and 1694 (two $COOCH_3$); 1630 cm^{-1} (diaryl ketone CO). PMR spectrum ($CDCl_3$, hexamethyldisiloxane), δ: 8.45 and 7.60 (d, J = 9.0 Hz, 1H each, 5-H and 4-H), 7.92 (q, 2H, o-H relative to CO), 6.90-7.65 (m, aromatic H), 3.92 (s, 2H, CH_2), and 3.82 and 3.25 ppm (s, 3H each, $COOCH_3$). Found: N 3.2%; M^+ 425. $C_{26}H_{19}NO_5$. Calculated: N 3.3%; M 425.

5-Oxo-2-phenylindeno[2,3-f]indolizine (XI). A) Quaternary salt X was obtained in 67% yield from equimolar amounts of 3-methyl-2-azafluorenone and bromoacetophenone in acetonitrile at 50°C; the dark-green crystals had mp 298-300°C. IR spectrum: 1709 (9-CO) and 1694 cm^{-1} (phenacyl CO). PMR spectrum (CD_3OD, hexamethyldisiloxane), δ: 9.01 (s, 1H, 1-H), 8.51 (s, 1H, 4-H), 7.50-8.37 (m, 9H, aromatic), 6.45 (s, 2H, N^+-CH_2), and 2.80 ppm (s, 3H, CH_3). PMR spectrum (0.03 N solution of CD_3ONa in CD_3OD), δ: 9.06 (s, 1H, 1-H), 8.56 (s, 1H, 4-H), and 7.50-8.40 ppm (m, 9H, aromatic). Found: C 64.0; H 3.8; Br 20.1; N 3.3%. $C_{21}H_{16}BrNO_2$. Calculated: C 64.0; H 4.0; Br 20.3; N 3.5%.

B) A 0.3-g (0.76 mmole) sample of bromide X was shaken with 15 ml of a 20% solution of potassium carbonate, and the resulting dark-brown crystals were dissolved in 10 ml of chloroform. The solution was filtered through a layer of aluminum oxide, the solvent was removed from the filtrate by distillation, and the residue was triturated in ether to give 0.1 g (41%) of indenoindolizine XI as a brown powder with mp 236-238°C. IR spectrum (mineral oil): 1698 cm^{-1} (CO). PMR spectrum (CF_3COOH, TMS), δ: 9.56 (s, 1H, 1-H), 7.75-8.60 (m, 11H, aromatic), and 6.30 (s, 2H, 3-CH_2). PMR spectrum (CF_3COOD, TMS), δ: 9.54 (s, 1H, 1-H), and 7.75-8.52 ppm (m, 11H, aromatic). Found: C 85.8; H 4.8; N 4.7%; M^+ 295. $C_{21}H_{13}NO$. Calculated: C 85.4; H 5.0; N 4.8%; M 295.

C) A 0.5-g (1.3 mmole) sample of bromide X was refluxed for 4 h with a solution of 0.6 g (4.3 mmole) of potassium carbonate in 2 ml of water, and the resulting crystals were washed with water, dried over P_2O_5 (0.35 g, mp 234-236°C), and dissolved in a mixture of benzene and chloroform (5:1). The solution was filtered through a layer of aluminum oxide (15 g, 2.5 by 2.5 cm), and the bulk of the solvents was removed by distillation to give 0.16 g (47%) of orange plates of indenoindolizine XI with mp 247-248°C. Found: C 85.2; H 5.5; N 4.4%; M^+ 295. $C_{21}H_{13}NO$. Calculated: C 85.4; H 5.0; N 4.8%; M 295.

9-Oxo-3-methyl-2-azafluorenium Dibenzoylmethylid (XII). Water (6 ml), 10 ml of chloroform, 0.31 g (2 mmole) of benzoyl chloride, and 1 ml of a 40% solution of potassium carbonate were added successively to 0.4 g (1 mmole) of bromide X, after which the mixture was shaken for 20 min as nitrogen was bubbled through it. The solution was filtered through a layer of aluminum oxide, and the residue (0.2 g) from the chloroform solution was triturated in ether and dried over phosphorus pentoxide to give 0.15 g (37%) of brown crystals of dibenzoylmethylid XII with mp 177-180°C. Found: C 79.7; H 3.7; N 2.8%. $C_{28}H_{19}NO_3$. Calculated: C 80.5; H 4.5; N 3.3%.

5-Oxo-2-phenyl-3-benzoylindeno[2,3-f]indolizine (XIII). A mixture of 0.19 g (0.65 mmole) of indolizine XI, 1.9 g (8.4 mmole) of benzoic anhydride, and 0.19 g (1.32 mmole) of sodium benzoate was shaken at 140-150°C for 2 h, after which it was cooled, and the solid mass was triturated in 5 ml of 20% sodium hydroxide. The resulting black precipitate (0.16 g) was dissolved in benzene, and the hot solution was filtered through a layer of aluminum oxide (4 g). Partial evaporation of the filtrate yielded 0.1 g (40%) of indeno-indolizine XIII as an orange powder with mp 269-270°C. IR spectrum: 1705 (azafluorenone CO), 1640 (diaryl ketone CO), and 1605 cm^{-1} (broad s, aromatic C—C). Found: C 83.9; H 4.4; N 3.6%; M^+ 399. $C_{28}H_{17}NO_2$. Calculated: C 84.2; H 4.3; N 3.5%; M 399.

LITERATURE CITED

1. N. S. Prostakov, V. I. Kuznetsov, A. A. Savina, and M. A. Ryashentseva, Khim. Geterotsikl. Soedin., No. 5, 646 (1977).
2. N. S. Prostakov, L. A. Gaivoronskaya, M. S. M. Kamara, V. P. Zvolinskii, A. A. Savina, M. Makhsida, and V. U. Karrasko, Khim. Geterotsikl. Soedin., No. 4, 506 (1976).
3. N. S. Prostakov and O. B. Baktibaev, Khim. Geterotsikl. Soedin., No. 10, 1395 (1971).
4. A. E. Chichibabin, Zh. Russ. Fiz.-Khim. Ova, 59, 477 (1927).
5. W. Z. F. Armarego, J. Chem. Soc., B, 191 (1966).
6. E. T. Borrows, O. D. Holand, and J. Kenyon, J. Chem. Soc., B, 1069 (1946).
7. N. S. Prostakov, A. V. Varlamov, G. A. Vasil'ev, O. G. Kesarev, and G. U. Alvarado, Khim. Geterotsikl. Soedin., No. 1, 124 (1977).