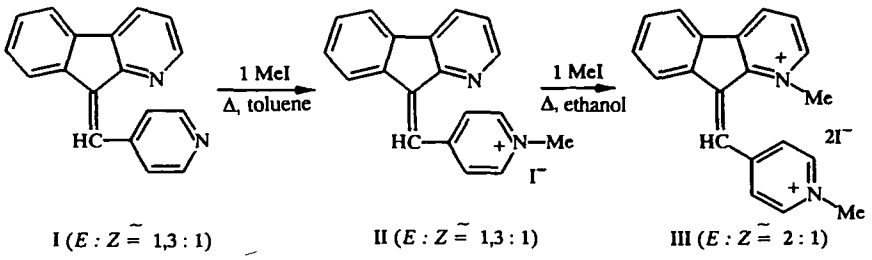
Chemistry of Heterocyclic Compounds, Vol. 34, No. 8, 1998

SYNTHESIS OF QUATERNARY SALTS, ANHYDROBASES, AND 9-(1,2-DIMETHOXYCARBONYL-3-BENZOYL-7-INDOLIZINYL-METHYLENE)-4-AZAFLUORENE BASED ON 9-(γ-PYRIDYLMETHYLENE)AZAFLUORENES

N. M. Kolyadina, A. T. Soldatenkov, O. M. Baktibaev, and N. S. Prostakov

The ratios of E- *to* Z-*isomers of the quaternary salts prepared by mono- and diquaternization of 9-(γ-pyridylmethylene)-1-(4)-azafluorenes with iodomethane or bromoacetophenone have been determined. Conversion of the diphenacyl 9-(γ-pyridyl)-4-azafluorenium bromide into the corresponding anhydrobase (diylide), and also its condensation with acetylenedicarboxylate diesters to give 9-(1,2-dimethoxycarbonyl-3-benzoyl-7-indolizinylmethylene)-4-azafluorene have been carried out.*

9-(γ-Pyridylmethylene)-1- and -4-azafluorenes contain two centers for electrophilic addition of alkyl halides, but for attack carbocations the most sterically suitable and clearly more basic is the nitrogen atom of the γ-pyridyl substituent. We have confirmed this by reaction of mixtures of the geometric isomers of 9-(γ-pyridylmethylene)-1-azafluorene (I), prepared by a known method [1], with one equivalent of methyl iodide. Quaternization occurred at the nitrogen atom of the γ-pyridine group and did not depend on the *Z*- or *E*-configuration of the fluorene starting material I.



I (*E* : *Z* ≈ 1,3 : 1) II (*E* : *Z* ≈ 1,3 : 1) III (*E* : *Z* ≈ 2 : 1)

A high yield (82%) of a mixture of the iodomethylates of (*E,Z*) 9-(γ-pyridylmethylene)-1-azafluorene (II) was obtained with a ratio of the *E*- and *Z*-isomers of 1.3:1, which was practically the same as in the starting material I. Quaternization of the pyridine ring was confirmed by the ^{1}H NMR spectrum which showed by a weak field shift (Δδ 0.4 ppm relative to the spectrum of the fluorene starting material I) of the signals of the two α-protons and the two β-protons of the pyridine substituent. Other peculiarities of the ^{1}H NMR spectra of these salts should be noted. For example, proton 10-H is sensitive to quaternization and gives an overall singlet signal of unit intensity at very weak field (9.0 ppm) for both isomers, whereas in the starting material I it resonates at 7.5 (*Z*-isomer) and 8.0 ppm (*E*-isomer). The aromatic protons of the azafluorene unit have a multiplicity and chemical shifts which are practically the same as those of compound I. In fact the only signals in salts II which are characteristically different for the *Z*- and *E*-isomers are those of the N−CH_3 group at 4.55 for the *E*-isomer and 4.50 ppm for the *Z*-isomer.

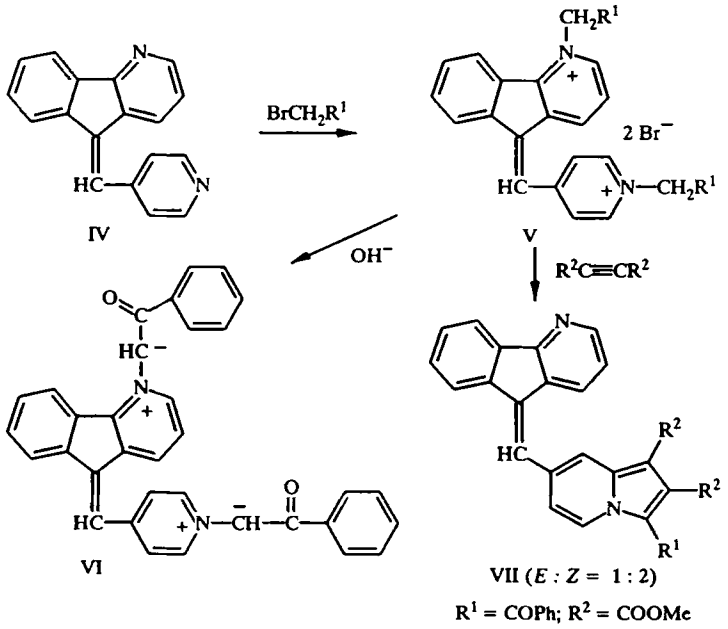
A steady conversion of the *E*-isomer of II into the *Z*-isomer was observed in the ^{1}H NMR spectrum of a DMSO-D_6 solution. In the temperature range 60-120°C the *E*:Z ratio was about 1.3:1.0, at 140°C about 1.1:1.0 and at 160°C about 0.8:1.0.

Russian University for Friendly Nations, Moscow 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1088-1092, August, 1998. Original article submitted October 31, 1997.

0009-3122/98/3408-0937$20.00 ©1999 Kluwer Academic/Plenum Publishers

The two isomers were not separated by crystallization. In this connection an attempt was made to convert the *E*-isomer into the diiodide *E*-III based on the premise that, because of great steric hindrance, the *Z*-isomer could not form the corresponding diiodide and therefore could be isolated in the pure form. However, when the monoiodide (*E*:*Z* 1.3:1) was heated with MeI in ethanol both isomers were quaternized. The ratio of the *E*- and *Z*-isomers in the mixture of diiodides isolated was about 2:1 as determined from the integrated intensities of the methyl singlets (at 4.46 and 4.43 for the *Z*-isomer and at 3.75 and 3.72 ppm for the *E*-isomer). Thus despite the enrichment of the *E*-isomer in diiodide III, a considerable amount of the sterically disadvantaged *Z*-isomer of III was formed which may be connected not only with direct quaternization of the monosalt *Z*-II to *Z*-III, but also the possibility of the isomerization of *E*-III → *Z*-III by the addition-elimination reaction of small amounts of iodine impurity at the $C_{(9)}=C_{(10)}$ bond.

The quaternary salt V was formed in 60% yield by the reaction of 9-(γ-pyridylmethylene)-4-azafluorene (IV) (*E*:*Z* 1:2) with two equivalents of bromoacetophenone. Treatment of V with potassium carbonate in acetonitrile gave a high yield of the anhydrobase in the form of the diylide VI (a deep cinnamon powder which gave a clear red solution in acetonitrile). Signals for the CH_2 group were absence from the ^1H NMR spectrum but three groups of signals at 8.6, 7.9 and 7.4 with relative integrated intensities of about 3:10:11 were observed in the aromatic proton region. These signals were unresolved and broadened by solvation of the zwitterion.



The IR spectrum of the diylide VI contains two strongly differentiated bands in the carbonyl absorption region. The typical benzoylmethylene fragment in the pyridine substituent $^+N(_{1'})-CH-C^--O$, in which the negative charge is delocalized to the α-carbonyl group, absorbs at 1666 cm^{-1}, the region common for similar ylides [2-4]. The absorption of the analogous ylide group at $N_{(4)}$ of the azafluorene ring does not undergo the expected shift to shorter wavelength — it absorbs in the region typical for ketones at 1710 cm^{-1}. In the latter case the carbonyl group in the chain is evidently not conjugated with the ylide unit because of steric hindrance and the negative of this ylide remains localized on the carbon atom: $-CO-C^--H-N^+$.

The structure of the diylide VI was also confirmed from its mass spectrum in which low intensity peaks for the ions $[M-H]^+$ and $[M-COPh]^+$ were observed in addition to the molecular ion M^+ with m/z = 492 (3%).

Azafluorenium phenacyl salts are known to undergo 1,3-dipolar cycloaddition with diesters of acetylenedicarboxylic acid in the presence of base to give indenoindolizines via a phenacylmethylide intermediate [5, 6]. In the case of the double salt V, the generation of two methylide fragments which differ in steric surroundings and localization of the negative charge may affect the expected direction of the reaction with the acetylenedicarboxylate esters. In fact condensation of salt V with two equivalents of the ester in the presence of triethylamine caused elimination of the phenacyl group at the $N_{(4)}$ nitrogen atom of the azafluorene unit and 1,3-cycloaddition of one molecule of the acetylenedicarboxylate ester at the phenacylpyridine substituent. As a result 9-(1,2-dimethoxycarbonyl-3-benzoylindolizin-7-yl)methylene-4-azafluorene (VII) was isolated in 42%

yield with an *E*:*Z* ratio of 1:2 (from ^{1}H NMR data), which is close to the ratio in the initial fulvene IV. The pure Z-isomer was isolated by crystallization from the mixture of isomers. Its IR spectrum contained two sharp intense C=O absorptions from the two carbomethoxy substituents at 1723 and 1683 cm^{-1} and one broad band at 1687 cm^{-1} ascribed to the carbonyl of the benzoyl radical.

The presence in the ^{1}H NMR spectrum of Z-VII of signals for the 2-H and 3-H protons at 7.03 and 8.55 ppm, which are similar in chemical shift to the corresponding protons in the Z-isomer of IV [1], indicates that the acetylenecarboxylate ester added to the pyridine group. Signals of the aromatic protons 5′-H, 6′-H, and 8′-H of the indolizine fragment underwent a weak field shift and appear at 9.61, 8.01, and 8.69 ppm respectively. The two methyl groups of the Z-isomer of VII resonate at 3.81 and 3.55 ppm (in the *E*-isomer of VII they give signals at 3.7 and 3.25 ppm in the ^{1}H NMR spectrum of the mixture of *E*- and Z-VII).

It has therefore been established that the diphenacyldibromide of 9-(γ-pyridylmethylene)-1-azafluorene reacts with dimethyl acetylenedicarboxylate in the presence of triethylamine by addition of the dipolarophile at the phenacyl group on the pyridine unit while the phenacyl group at nitrogen atom $N_{(4)}$ of the azafluorene group is lost. This elimination is evidently associated with two factors: steric hindrance, confirmed by a Dreiding model, and decreased stability of the $-HC-{}^+N_{(4)}$ bond because of delocalization of the negative charge as indicated by the IR spectrum of the diylide VI discussed above.

The quaternary salts II, III and IV were tested as fungicides for plants. In all tests *in vitro* and *in vivo* with phytophthora infection of tomatoes they were inactive, whereas they had notable fungicidal effects on powdery mildew of cucumbers at a concentration of 11% (compounds II and III) and 23% (compound V) and also decreased the toxicity of grey rot of pulses at concentrations of 56, 35 and 47% respectively.

EXPERIMENTAL

^{1}H NMR Spectra were recorded with a Bruker WP-80 machine in DMSO-D_6 with TMS as internal standard. Mass spectra were recorded on an MX-1303 spectrometer with an ionizing voltage of 70 eV. IR spectra of KBr discs were recorded on a UR-20 instrument. Electronic absorption spectra of ethanol solutions were measured with a Specord UV-vis spectrophotometer. The course of reactions and the purity of free bases were monitored by TLC on Silufol UV-254 strips; detection was with iodine vapor.

9-(γ-(N-Methyl)pyridylmethylene)-1-azafluorene Iodide (II). A solution of 9-(γ-pyridylmethylene)-1-azafluorene I (1:3 ratio of *E*:*Z* isomers) (1.3 g, 5.1 mmole) and methyl iodide (5 ml) in absolute toluene (50 ml) was boiled for 30 min and kept at 20°C for 24 h. The precipitate was separated and washed with toluene followed by ether to give the quaternary monosalt II as red-brown powder (1.7 g, 82%), mp 193-195°C (dec). Found (%): C 57.2, H 4.0, N 6.7. Calc. for $C_{19}H_{15}IN_2$ (%): C 57.3, H 3.8, N 7.0. M 398. ^{1}H NMR Spectrum: 9.1 (2H, br. d, J = 5.3 Hz, 2′-H, 6′-H), 9.0 (1H, s, 10-H), 8.53 (1H, d.d., J = 5.0 and 1.5 Hz, 2-H), 8.38 (2H, d.d., J = 5.3 and 1.0 Hz, 3′-H, 5′-H), 8.13 (1H, m, 5-H), 7.95 (1H, m, 8-H), 4.55 and 4.50 ppm (both singlets, 1.7 and 1.3 H respectively, $^+N-CH_3$ of the *E*- and Z-isomers respectively).

1-Methyl-9[(γ-(N-methyl)pyridylmethylene]-1-azafluorenium Diodide (III). Methyl iodide (7 ml) was added to a solution of monosalt II (0.8 g, 2 mmole) in absolute ethanol (50 ml), the mixture was boiled for 1 h, then kept at 20°C for 24 h. The precipitate was removed and washed with cold ethanol (5 ml) and ether to give red-brown needles of diiodide (III) (0.68 g, 63%), mp 205-207°C (dec). Found (%): C 44.4, H 3.4, N 5.5. Calc. for $C_{20}H_{18}I_2N_2$ (%): C 44.4, H 3.4, N 5.2. M 540. ^{1}H NMR Spectrum: 9.1 (2H, br.d., J = 5.1 Hz, 2′-H, 6′-H) 9.03 (1H, s, 10-H), 8.48 (1H, d.d., J = 5.0 and 1.8 Hz, 2-H), 8.38 (2H, d.d., J = 5.1 and 1.6 Hz, 3′-H, 5′-H), 8.13 (1H, m, 5-H), 7.95 (1H, m, 8-H), 4.46 and 4.43 (both singlets, 1H and 2H respectively, $^+N_{(1')}-CH_3$ of the *E*- and Z-isomers respectively), 3.75 and 3.72 ppm (both singlets, 1H and 2H respectively, $^+N_{(1)}-CH_3$ of the *E*- and Z-isomers respectively.)

4,1′-Diphenacyl-9-(γ-pyridylmethylene)-1-azafluorenium Dibromide (V). A solution of 9-(γ-pyridylmethylene)-1-azafluorene (IV) (ratio of *E*- to Z-isomers 1:2 [1]) (0.73 g, 2.8 mmole) and bromoacetophenone (1.12 g, 5.63 mmole) in acetone (30 ml) was boiled for 7 h and left for 1 day at 20°C. The precipitate was separated and washed with ether to give dibromide V as a yellowish powder (1.1 g, 60%), mp 160-161°C (dec). Found (%): C 62.5, H 3.9, N 4.5. Calc. for $C_{34}H_{26}Br_2N_2O_2$ (%): C 62.4, H 4.0, N 4.3. M 654. IR Spectrum: 1796 and 1687 s (C=O), 1630 br. s, 1620 cm^{-1} sh (C=C).

9-(γ-Pyridylmethylene)-1-azafluorenium 1′,4-di(benzoylmethylide) (VI). A saturated solution of K_2CO_3 in CH_3CN (1 ml) was added to a solution of salt V (40 mg, 0.06 mmole) in CH_3CN (1 ml) at 14°C and the mixture was stirred for 5 min.

The solvent was removed in vacuum and the residue washed with water to give the diylide VI as a red brown-powder (24 mg, 80%), mp 84-85°C (dec). UV Spectrum (CH_3CN), λ_{max}: 322 (sh), 340, 353, 490, 526 nm. IR Spectrum: 1666 ($^+N_{(1')}-CH-C-O$), 1710 cm^{-1} ($^+N_{(4)}-CH-C-O$). ^1H NMR Spectrum: 8.6 (3H, α-H, pyridine), 7.9 (10H, m, arom-H and 10-H), 7.4 ppm (11H, m, arom-H and $^+N-CH-CO$). Mass Spectrum, *m/z* (%): M^+ 492 (3), $[M-H]^+$ 491 (2), $[M-COPh]^+$ 387 (7), $[M-H-2^{\bullet}\ COPh]^+$ 281 (4). Found (%): C 62.5, H 3.9, N 4.5. Calc. for $C_{34}H_{24}N_2O_2$ (%): C 62.4, H 4.0, N 4.3. M 492.

9-(1,2-Dimethoxycarbonyl-3-benzoindolizin-7-yl)methylene-4-azafluorene (VII). A solution of dimethyl acetylenedicarboxylate (0.28 g, 0.25 ml, 2 mmole) in $CHCl_3$ (3 ml) followed by a solution of triethylamine (0.36 ml, 2.5 mmole) in $CHCl_3$ (3 ml) was added to a stirred solution of salt V (0.65 g, 1 mmole) in $CHCl_3$ (10 ml) at 20°C. The mixture was stirred for 4 h at 50°C and then kept at 20°C for 24 h. The chloroform was evaporated off and the residue chromatographed on a silica column with hexane as eluent to give indolizine VII as yellow crystals (ratio of *E*- to *Z*-isomers 1:2 according to ^1H NMR spectrum (0.22 g, 42.3%). The pure Z-isomer VII (12 mg, 3%) was isolated as yellow crystals by recrystallization from hexane, mp 189-190°C (dec). Found (%): C 74.5, H 4.2, N 5.0. M^+ 514. Calc. for $C_{32}H_{22}N_2O_5$ (%): C 74.7, H 4.3, N 5.5. IR Spectrum: 1723 and 1683 (C=O, methoxycarbonyl), 1687 and 1680 cm^{-1} sh (C=O, benzoyl group). ^1H NMR Spectrum: 9.61 (1H, d, J = 6.0 Hz, 5'-H), 8.69 (1H, br. s, 8'-H), 8.55 (1H, d.d., J = 5.2 and 1.8 Hz, 3-H); 8.23 (1H, d.d., J = 8.0 and 1.8 Hz, 1-H); 8.01 (1H, d.d., J = 6.0 and 1.5 Hz, 6'-H), 7.80-7.40 (11H, arom-H), 7.35 (1H, s, 10-H), 7.17 (1H, q, 2-H), 3.81 (3H, s, CH_3), 3.35 ppm (3H, s, CH_3). In the ^1H NMR spectrum of the mixture of isomers of VII the CH_3 protons resonate at 3.7 and 3.25 ppm. Mass spectrum, *m/z* (%): M^+ 514 (100), 491 (6), $[M-COMe]^{+\cdot}$ 455 (3), $[M-Ph]^{+\cdot}$ 437 (5), $[M-COPh]^{+\cdot}$ 409 (2), 379 (6), 261 (4), 233 (3), 193 (11), 163 (5), $[COPh]^{+\cdot}$ 105 (14), 77 (18), $[COOMe]^{+\cdot}$ 59 (10).

The authors thank E. I. Andreeva for carrying out the biological testing and providing the results.

This work was supported by grant FT-15 for Fine Organic Synthesis from VO NTP GKRF.

REFERENCES

1. N. M. Kolyadina, L. A. Murugova, A. T. Soldatenkov, A. A. Ustenko, and N. S. Prostakov, Khim. Geterotsikl. Soedin., No. 11, 1513 (1992).
2. I. Zugravcesku and V. Petrovanu, N-Ylid Chemistry, McGraw-Hill, New York (1976), p. 168.
3. G. Surpateanu, J. P. Catteau, P. Karafilogiu, and A. Lablach Combier, Tetrahedron, **32**, 2647 (1976).
4. N. S. Prostakov, A. P. Krapivko, A. T. Soldatenkov, A. A. Savina, and I. Romero, Khim. Geterotsikl. Soedin., No. 3, 384 (1979).
5. N. S. Prostakov, L. A. Gaivoronskaya, R. Anastasi, M. S. M. Kamara, and A. A. Savina, Khim. Geterotsikl. Soedin., No. 6, 794 (1979).
6. N. S. Prostakov, A. T. Soldatenkov, and P. K. Radzhan, Khim. Geterotsikl. Soedin., No. 5, 706 (1982)