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Synthesis of Pyrrolizidine- and Indolizidinedione Derivatives Based on *N*-Phthalylaspartic Acid

I. M. Sakhautdinov, N. A. Leont'eva, F. Z. Galin, and G. F. Vafina

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, Ufa, 450054 Russia
e-mail: vafina@anrb.ru

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Abstract—A procedure was developed for the synthesis of pyrrolizidine- and indolizidinediones derivatives from the keto-stabilized sulfonium α- and β-ylides of *N*-phthalylaspartic acid.

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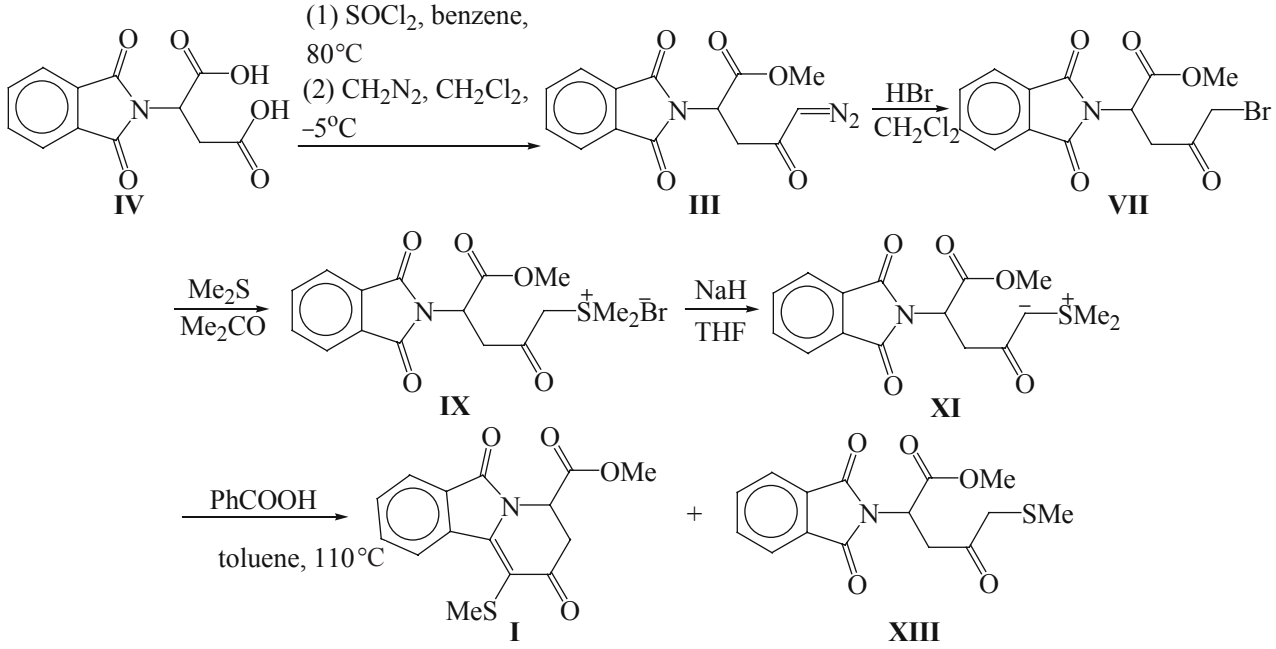
Derivatives of pyrrolizidine- and indolizidinediones possess important pharmacological properties [1]. The most prominent among these compounds are naturally occurring alkaloids like campotothecin, mappicin, and mappicin-ketone that take a significant place among the oncological and cardiological drugs. All of them contain in their structure a pyrrolo[3,4-*b*]-quinoline skeleton.

We showed formerly [2–5] that keto-stabilized sulfonium ylides, derivatives of N-protected α- and β-amino acids, readily enter into reactions of intramolecular cyclization. The intramolecular cyclization of ylides makes it possible to synthesize alkaloids and alkaloid-like substances. No doubt that among organosulfur heterocycles obtained through ylides new biologically active compounds would be discovered. In extension of research on the intramolecular cyclization we carried out preparation of products possessing indolizidine- and pyrrolizidinedione structure proceeding from the keto-stabilized sulfonium ylides obtained from *N*-phthalyl-aspartic acid.

The synthesis of a compound of indolizidinedione structure **I** was performed starting from diazoketone **III**

Scheme 1.



obtained by Arndt–Eistert reaction from *N*-phthalylaspartic acid (**IV**) (Scheme 1).

For the synthesis of a compound of pyrrolizidinedione structure **II** we analogously prepared α-diazoketone **V** from N-phthalylaspartic acid β-methyl ester (**VI**) (Scheme 2).

The structure of diazoketones **III** and **V** was confirmed by their spectral characteristics. A characteristic feature of the IR spectra is the presence of strong absorption bands of diazo group at ν 2110 cm^{-1} for diazoketone **III** and 2125 cm^{-1} for diazoketone **V**. In the ^{13}C NMR spectra the carbon signals from the CHN_2 group appear at δ 47.8 ppm for compound **III** and 52.64 ppm for compound **V**. In the ^{1}H NMR spectra the singlet signal of the proton from the CHN_2 group is observed at δ 5.32 ppm for diazoketone **III**, 5.39 ppm for diazoketone **V**. Diazoketones **III** and **V** were treated with water solution of HBr to obtain bromomethyl ketones **VII** and **VIII** whose reaction with Me_2S resulted in sulfonium salts **IX** and **X**. The deprotonation of these salts with sodium hydride in THF under an argon atmosphere provided keto-stabilized sulfur ylides **XI** and **XII** respectively.

The structure of all compounds obtained was confirmed by spectral methods. In the ^{13}C NMR spectra of bromomethyl ketones **VII** and **VIII** informative signals were those of the methylene carbon atom in the CH_2Br group appearing at δ 34.08 ppm for compound **VII** and at 30.54 ppm for bromomethyl ketone **VIII**.

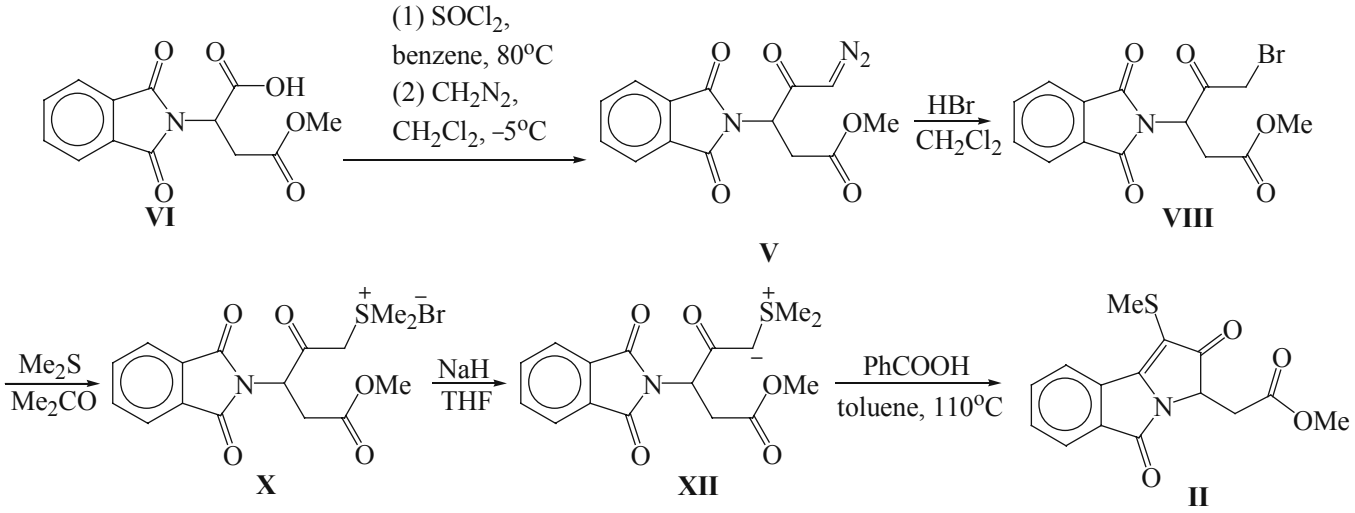
It should be noted that the obtained ylides are unstable and quickly decompose already at room temperature, therefore it is difficult to register the spectra of pure ylides. However their formation can be observed in the IR spectrum by the shift of the absorption band of the carbonyl linked to anion to the long-wave region characteristic of keto-stabilized ylides (ν 1540 cm^{-1}). The formation of ylides was confirmed also by elemental analysis performed just after their preparation.

The heating of sulfur ylides **XI** and **XII** in boiling toluene with an equimolar quantity of benzoic acid resulted in formation of compounds with indolizidinedione structure **I** and pyrrolizidinedione structure **II** respectively. In this reaction from compound **XI** formed also linear sulfide **XIII** in 10% yield.

The structures of compounds **I** and **II** were confirmed by NMR spectra. For instance, in the ^{1}H NMR spectrum an informative feature is the distortion of the symmetry of two multiplet signals from the four protons of the phthalyl fragment in the region δ 7.68–9.08 ppm for compound **I**, 7.65–8.25 ppm for compound **II**, and the appearance of a characteristic three-proton singlet from thiomethyl group in the region δ 2.38 ppm for compound **I**, 2.55 ppm for compound **II**. In the ^{13}C NMR spectra the signal from MeS group is observed at δ 17.88 ppm for compound **I**, 15.57 ppm for compound **II**.

Thus along the above described procedures we succeeded to perform the reaction in the case of aspartic acid both at the α- and the β-carboxy groups. It was also interesting to carry out the reaction at both carboxy groups simultaneously. However the attempts to prepare didiazoketone were unsuccessful. In order to prepare *N*-phthaloylaspartic acid dichloride we carried out reac-

Scheme 2.



tions of compound **IV** with phosphorus pentachloride, methyl chloroformate, and oxalyl chloride. From the reactions with methyl chloroformate and oxalyl chloride acid **IV** was recovered intact. In reaction of compound **IV** with PCl_5 a small amount of *N*-phthaloyl-substituted aspartic acid anhydride was obtained which under the treatment with diazomethane formed β-diazoketone **III**. No formation of acid dichloride and consequently of didiazoketone occurred.

Thus we synthesized new compounds of indolizidine-**I** and pyrrolizidinedione **II** structures from keto-stabilized sulfonium ylides obtained based on *N*-phthaloylaspartic acid.

EXPERIMENTAL

IR spectra were recorded on spectrophotometers UR-20 and Specord M 80 from thin films or mulls in mineral oil. ^1H and ^{13}C NMR spectra were registered from solutions in $CDCl_3$ on a spectrometer Bruker-AM 300 at operating frequencies 300.13 and 75.25 MHz respectively, internal reference TMS, for ^1H spectra also HMDS. The reaction progress was monitored by TLC on plates Sorbfil PTAKh-AF-A (Krasnodar), spots were visualized under UV irradiation, in iodine vapor, by spraying the plates with a solution of ninhydrin developer or with solution of anisaldehyde followed by heating at 100–120°C. Reaction products were isolated by column chromatography on silica gel (eluent petroleum ether–ethyl acetate, 4:1).

2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-succinic acid (**IV**) and 2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-methoxy-4-oxobutanoic acid (**VI**) were prepared by known procedures [6].

Diazo compounds III and V. General procedure. To a dispersion of 5.26 g (20 mmol) of phthaloyl-protected acid in 100 ml of anhydrous benzene was added 3.6 ml (50 mmol) of thionyl chloride, and the mixture was boiled to the end of gas liberation (~3 h). On distilling off benzene and excess thionyl chloride the obtained acid chloride was used in reaction with CH_2N_2 without additional purification. The solution of 2.8 g (10 mmol) of the acid chloride in 20 ml of CH_2Cl_2 was added dropwise while stirring to the cooled to –5°C solution of diazomethane prepared from 10 g (40 mmol) of nitrosomethylurea. The reaction mixture was stirred at this temperature for 30 min and then left standing in a refrigerator for 12 h. The solvent was evaporated, the diazoketones were isolated by column chromatography.

Methyl 5-diazo-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-oxopentanoate (III). Yield 3.01 g (50%), yellow oily substance. IR spectrum, ν, cm^{-1}: 1630, 1710, 1770, 2110. ^1H NMR spectrum, δ, ppm: 3.12–3.43 m (2H, CH_2), 3.72 s (3H, CH_3), 5.32 s (1H, CHN_2), 5.47–5.59 m (1H, CH), 7.69–7.92 m (4H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 39.16 (CH_2), 47.80 (CHN_2), 53.02 (OCH_3), 55.28 (CH), 123.56 (CH_{arom}), 131.68 (C_{arom}), 134.22 (CH_{arom}), 167.23 (C=O), 169.08 ($C=O_{phthalyl}$), 189.9 ($C=O_{phthalyl}$), 204.94 (C=O). Found, %: C 55.81; H 3.66; N 13.94. $C_{14}H_{11}N_3O_5$. Calculated, %: C 55.81; H 3.65; N 13.95.

Methyl 5-diazo-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-oxopentanoate (V). Yield 2.71 g (45%), light-yellow crystals, mp 72–75°C. IR spectrum, ν, cm^{-1}: 1660, 1710, 1725, 2125. ^1H NMR spectrum, δ, ppm: 2.92–3.38 m (2H, CH_2), 3.58 s (3H, CH_3), 5.18–5.25 m (1H, CH), 5.39 s (1H, CHN_2) 7.69–7.87 m (4H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 32.44 (CH_2), 51.96 (OCH_3), 52.64 (CHN_2), 54.0 (CH), 123.66 (CH_{arom}), 131.42 (C_{arom}), 134.45 (CH_{arom}), 167.14 ($C=O_{phthalyl}$), 170.76 (C=O), 188.25 (C=O). Found, %: C 55.81; H 3.65; N 13.96. $C_{14}H_{11}N_3O_5$. Calculated, %: C 55.81; H 3.65; N 13.95.

Bromomethyl ketones VII and VIII. *General procedure.* To a solution of 0.3 g (1 mmol) of diazoketone in 10 ml of dichloromethane was added at stirring 1 ml of 48% water solution of HBr. After the end of gas liberation the solution was stirred for 1 h, then the organic layer was separated, washed with 5% sodium carbonate solution, and dried with $MgSO_4$. On evaporating the solvent the residue was purified by chromatography.

Methyl-5-bromo-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-oxopentanoate (VII). Yield 0.27 g (77%), yellow oily substance. IR spectrum, ν, cm^{-1}: 1720, 1780. ^1H NMR spectrum, δ, ppm: 3.28–3.39 m (2H, CH_2), 3.75 s (3H, CH_3), 3.95–4.0 d (2H, $BrCH_2$, *J* 6 Hz), 5.47–5.55 m (1H, CH), 7.72–7.94 m (4H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 34.079 (CH_2Br), 39.022 (CH_2), 47.624 (CH), 53.142 (OCH_3), 123.622 (CH_{arom}), 131.574 (C_{arom}), 134.334 (CH_{arom}), 167.119 (C=O), 168.940 ($C=O_{phthalyl}$), 197.938 (C=O). Found, %: C 47.46; H 3.38; Br 22.54; N 3.92. $C_{14}H_{12}BrNO_5$. Calculated, %: C 47.46; H 3.39; Br 22.6; N 3.95.

Methyl-5-bromo-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-oxopentanoate (VIII). Yield 0.26 g

(74%), colorless crystals, mp 102–104°C. IR spectrum, ν, cm^{-1}: 1710, 1770. ^1H NMR spectrum, δ, ppm: 2.83–3.36 m (2H, CH_2), 3.63 s (3H, CH_3), 3.85–4.0 d (2H, $BrCH_2$, *J* 13 Hz), 5.50–5.58 m (1H, CH), 7.73–7.91 m (4H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 30.54 (CH_2Br), 32.99 (CH_2), 52.18 (OCH_3), 52.36 (CH), 123.95 (CH_{arom}), 131.50 (C_{arom}), 134.69 (CH_{arom}), 167.18 ($C{=}O_{phthalyl}$), 170.34 (C=O), 195.92 (C=O). Found, %: C 47.46; H 3.40; Br 22.55; N 3.92. $C_{14}H_{12}BrNO_5$. Calculated, %: C 47.46; H 3.39; Br 22.6; N 3.95.

Sulfonium salts IX and X. *General procedure.* To a solution of 0.35 g (1 mmol) of bromoketone in 10 ml of anhydrous acetone was added at stirring 0.186 g (3 mmol) of dimethyl sulfide, and the mixture was left standing for 12 h. The solvent was decanted, and the precipitate was washed with acetone.

[4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-methoxy-2,5-dioxopentyl](dimethyl)sulfonium bromide (IX). Yield 0.32 g (78%), colorless crystals, mp 137–139°C. IR spectrum, ν, cm^{-1}: 1714, 1724, 1776. Found, %: C 46.25; H 4.35; Br 19.25; N 3.36; S 7.70. $C_{16}H_{18}BrNO_5S$. Calculated, %: C 46.15; H 4.33; Br 19.23; N 3.37; S 7.69.

[3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-methoxy-2,5-dioxopentyl](dimethyl)sulfonium bromide (X). Yield 0.27 g (65%), colorless crystals, mp 104–105°C. IR spectrum, ν, cm^{-1}: 1720, 1725, 1775. Found, %: C 46.15; H 4.34; Br 19.23; N 3.36; S 7.70. $C_{16}H_{18}BrNO_5S$. Calculated, %: C 46.15; H 4.33; Br 19.23; N 3.37; S 7.69.

Sulfur ylides XI and XII. *General procedure.* To a stirred dispersion of 1.248 g (3 mmol) of sulfonium salt in 10 ml of anhydrous THF at room temperature under an argon atmosphere was added in one portion 0.026 g (1.1 mmol) of sodium hydride. The reaction mixture was stirred for 30 min, filtered, dried with K_2CO_3, and the solvent was distilled off.

Methyl 5-(dimethyl-λ⁴-sulfanylidene)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-oxopentanoate (XI). Yield 0.59 g (59%), yellow oily substance. IR spectrum, ν, cm^{-1}: 1560, 1714, 1774. Found, %: C 57.33; H 5.09; N 4.19; S 9.57. $C_{16}H_{17}NO_5S$. Calculated, %: C 57.31; H 5.07; N 4.18; S 9.55.

Methyl 5-(dimethyl-λ⁴-sulfanylidene)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-oxopentanoate (XII). Yield 0.95 g (95%), yellow oily substance. IR spectrum, ν, cm^{-1}: 1560, 1710, 1775. Found, %: C 57.32; H 5.08; N 4.19; S 9.55. $C_{16}H_{17}NO_5S$. Calculated, %: C 57.31; H 5.07; N 4.18; S 9.55.

Intramolecular cyclization. In 8 ml of anhydrous toluene was dissolved at heating 0.67 g (2 mmol) of ylide, 0.244 g (2 mmol) of benzoic acid was added, and the mixture was boiled for 30 min. Then the solvent was distilled off, and the residue was subjected to chromatography.

Methyl 1-(methylthio)-2,6-dioxo-2,3,4,6-tetrahydropyrido[2,1-*a*]isoindol-4-carboxylate (I). Yield 0.44 g (72%), bright-yellow oily substance. IR spectrum, ν, cm^{-1}: 1718, 1729, 1778. ^1H NMR spectrum, δ, ppm: 2.38 s (3H, CH_3), 3.05–3.35 m (2H, CH_2), 3.75 s (3H, CH_3), 5.29–5.35 m (1H, CH), 7.68–9.08 m (4H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 17.877 (SCH_3), 37.982 (CH_2), 50.110 (OCH_3), 53.241 (CH), 113.574 (C=C), 124.258 (CH_{arom}), 127.954 (CH_{arom}), 128.936 (C=C), 129.860 (C_{arom}), 131.678 (CH_{arom}), 132.170 (CH_{arom}), 133.446 (C_{arom}), 167.177 (C=O), 168.968 ($C{=}O_{phthalyl}$), 188.551 (C=O). Found, %: C 59.40; H 4.28; N 4.62; S 10.55. $C_{15}H_{13}NO_4S$. Calculated, %: C 59.41; H 4.29; N 4.62; S 10.56.

Methyl 2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-(methylthio)-4-oxopentanoate (XIII). Yield 0.064 g (10%), yellow oily substance. IR spectrum, ν, cm^{-1}: 1721, 1733, 1765. ^1H NMR spectrum, δ, ppm: 2.04 s (3H, CH_3), 3.25–3.4 m (2H, CH_2), 3.65–3.8 m (2H, CH_2), 3.75 C (3H, CH_3), 5.49–5.55 m (1H, CH), 7.75–7.92 m (4H, C_6H_4). Found, %: C 56.08; H 4.67; N 4.35; S 9.98. $C_{15}H_{15}NO_5S$. Calculated, %: C 56.07; H 4.67; N 4.36; S 9.97.

Methyl {1-(methylthio)-2,5-dioxo-2,5-dihydro-3*H*-pyrrolo[2,1-*a*]isoindol-3-yl}acetate (II). Yield 0.53 g (88%), bright-yellow oily substance. IR spectrum, ν, cm^{-1}: 1719, 1778. ^1H NMR spectrum, δ, ppm: 2.55 s (3H, CH_3), 3.11–3.46 m (2H, CH_2), 3.62 s (3H, CH_3), 4.55–4.60 m (1H, CH), 7.65–8.25 m (4H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 15.57 (SCH_3), 33.91 (CH_2), 52.08 (OCH_3), 57.33 (CH), 112.58 (C_{arom}), 124.23 (CH_{arom}), 125.35 (CH_{arom}), 130.38 (C=C), 132.34 (C_{arom}), 132.70 (CH_{arom}), 132.89 (CH_{arom}), 161.80 (C=C), 161.86 ($C{=}O_{phthalyl}$), 169.60 (C=O), 198.40 (C=O). Found, %: C 59.41; H 4.28; N 4.62; S 10.56. $C_{15}H_{13}NO_4S$. Calculated, %: C 59.41; H 4.29; N 4.62; S 10.56.

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