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ELECTROPHILIC SUBSTITUTION IN A SERIES OF DERIVATIVES OF 5,6,7,8-TETRAHYDRO-2*a*,4*a*-DIAZACYCLOPENTA[*c*,*d*]AZULENE

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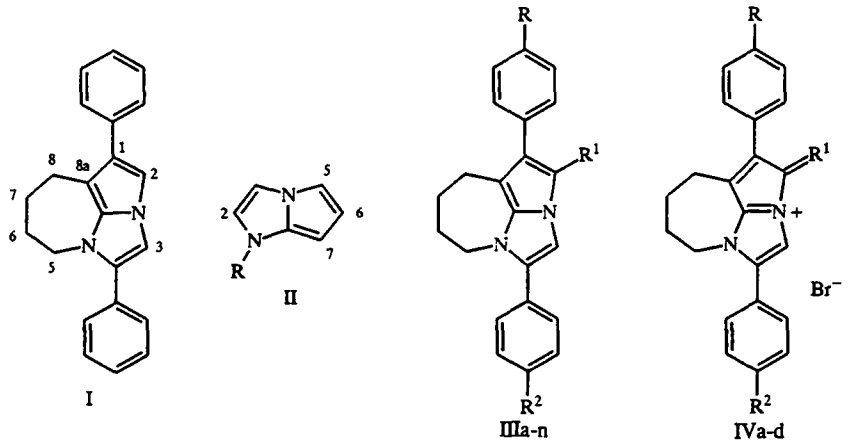
*Protonation, acylation, nitrosation, and addition of iso(thio)cyanates occur readily at position two of 1,4-diaryl-5,6,7,8-tetrahydro-*2a,4a*-diazacyclopenta[*c,d*]azulenes.*

The 1,4-diaryl-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c,d*]-azulenes (I) which we described comparatively recently [1] have similar electronic structures to the structurally similar derivatives of 1H-pyrrolo[1,2-*a*]imidazole (II) which were studied earlier [2].



III a,e,h,i,k,m R = OMe; b,f,j R = Br; c,g,e,n R = H; d R = Cl; a—c R^1 = H; d,R^1 = Me; e-g R^1 = COMe; h R^1 = CHO; i, j R^1 = CONHMe; k,*l* R^1 = $CSNHC_6H_4CF_3$-*m*; m,n R^1 = NO; a,d,e,g,i,k,m R^2 = Cl; b,c,f,g,j,*l*,n R^2 = OMe. IV a, d R = OMe; b R = Br; c R = H; a—c R^1 = 2H; d R^1 = $CHC_6H_4NMe_2$-*p*; a, d R^2 = Cl; b, c R^2 = OMe

We reached this conclusion on the basis of comparison of materials obtained using the GyperChem program [3] (belonging to the Institute of Organic Chemistry, National Academy of Sciences of Ukraine) to determine electron density distribution and bond orders in compounds I and II. Analysis showed that azulene can de described as a 10 π-electron heteroaromatic system in which the greatest *p*-electron density is localized on the carbon atoms of the pyrrole part of the tricycle and electrophilic attack should occur exclusively at the free position 2 of the system. The imidazole part of the tricycle and its position 3 in particular is deactivated relative to electrophilic attack. It therefore was of interest to prepare and investigate functional derivatives of 5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c,d*]azulene, which are otherwise not available by direct synthesis, by electrophilic substitution or addition.

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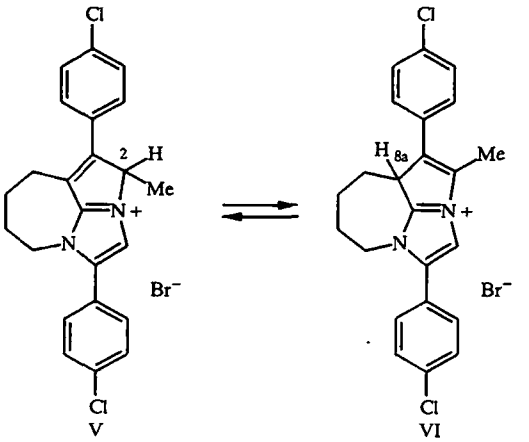
5,6,7,8-Tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulenes (IIIa-d) were unchanged on heating with 2 M sodium hydroxide solution or with 2M hydrochloric acid. With concentrated mineral acids, azulenes IIIa and IIIc formed stable salts IVa-c which were not hydrolyzed by water and were converted to the starting materials by alkali. The structures of the salts were readily determined by ^{1}H NMR spectroscopy. The appearance of a two proton singlet at 5.5 ppm indicated protonation of atom $C_{(2)}$, while the singlet of the 2-H proton at 6.7-6.9 ppm, characteristic of a base, disappeared. Proton 3-H, observed in base III in the 7.0-7.3 ppm region, underwent a weak field shift to the 8.1-8.2 ppm on conversion into the salt IV. Similar changes are characteristic of the change from the imidazole base to the imidazolium salt observed previously [4]. In cases where position $C_{(2)}$ is blocked by a substituent (e.g., azulene IIId), protonation occurs, to judge from the ^{1}H NMR spectra, to give salts V and VI, products of the addition of the proton to carbon atoms $C_{(2)}$ and $C_{(8a)}$.



Salts IIIa-c readily condense with aldehydes at the active methylene group at $C_{(2)}$. For example, we isolated the styryl dye IVd on condensation of 4-dimethylaminobenzaldehyde with salt IIIa. The simple salt from base IIId did not undergo condensation.

We studied a series of electrophilic substitutions and additions with a number of derivatives of 5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene III — acetylation, formylation, nitrosation and reactions with iso(thio)cyanates. These reactions occur under milder conditions than for the 1H-pyrrolo[1,2-*b*][1.2.4]triazole series [5] and are close to the conditions for the analogous reactions with the 4H-pyrrolo[1,2-*a*]benzimidazole series [6]. A characteristic of the acyl derivatives of the azulenes IIIe and IIIf is the absence of carbonyl bands in their IR spectra. This is explained by the major contribution of bipolar structures (negative charge localized on the oxygen atom and the positive charge on the junction nitrogen atom) to resonance stabilization of both the formyl and acetyl derivatives. The acetyl derivatives of the azulenes IIIe-g are readily hydrolyzed by mineral acids. On reaction of the azulenes III with isocyanates, N-substituted amides of the 5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene-2-carboxylic acids IIIi and j are formed, and with isothiocyanates the corresponding thioamides IIIk and *l*. These N-substituted amides and thioamides are very stable compounds. They are unchanged on heating with concentrated hydrochloric acid or ethanolic alkali.

EXPERIMENTAL

Corrected values of the melting points were determined with a Boetius block. IR spectra of KBr disks were measured with a Pye Unicam SP3-300 instrument. ^{1}H NMR spectra were determined with a Bruker WR-100 spectrometer (working frequency 100.13 MHz, TMS internal standard). UV spectra of $5\cdot10^{-5}$ M methanolic solutions were recorded with a Specord UV-vis machine. The purity of products was determined chromatographically on Silufol UV-254 plates with chloroform-methanol (9:1) as eluant.

1-(4′-Anisyl)-4-(4″-chlorophenyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacylopenta[*c*,*d*]azulene hydrobromide (IVa). The corresponding base I (0.6 g, 1.6 mmol) and concentrated hydrobromic acid (2 cm^3) were mixed and the viscous mass obtained was triturated to give colorless crystals. After dilution with water, the residue was filtered off, washed with water and purified by recrystallization from methanol–propanol-2 (1:5). Yield 0.71 g (97%). M.p. 260-261°C. ^{1}H NMR spectrum (DMSO-D_6): 5.54 (2 H, s, 2-CH_2), 8.20 (1 H, s, 3-H), 7.66 (4 H, s, arom), 7.61 and 7.10 (4 H, dd, arom), 4.15 (2 H, br.s, 5-CH_2), 3.83

(3 H, s, OCH_3), 2.95 (2 H, t, 8-CH_2), 2.17 (2 H, br.s, 6-CH_2), 2.0 ppm (2 H, s, 7-CH_2). IR spectrum: 3080, 2930 (C−H), 1650 cm^{-1} (C=N^+). Found, %: C 60.21, H 4.88, N 6.07. Calc. for $C_{23}H_{22}BrClN_2O$, %: C 60.34, H 4.84, N 6.12.

1-(4′-Bromophenyl)-4-(4″-anisyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene hydrobromide (IVb) was obtained in 92% yield analogously to IIIa. M.p. 272-273°C (from methanol). ^1H NMR spectrum (DMSO-D_6): 5.54 (2 H, s, 2-CH_2), 8.14 (1 H, s, 3-H), 7.66 and 7.59 (4 H, dd, arom), 7.56 and 7.12 (4 H, dd, arom), 4.12 (2 H, t, 5-CH_2), 2.83 (3 H, s, OCH_3), 2.93 (2 H, t, 8-CH_2), 2.17 (2 H, br.s, 6-CH_2), 1.99 ppm (2 H, s, 7-CH_2). IR spectrum: 3190, 2930 (C−H), 1650 cm^{-1} (C=N^+). Found, %: C 54.87, H 4.44, Br 31.68. Calc. for $C_{23}H_{22}Br_2N_2O$, %: C 55.0, H 4.42, Br 31.82.

1-Phenyl-4-(4′-anisyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene hydrobromide (IVc) was obtained in 96% yield analogously to IIIa. M.p. 252-256°C (from propanol-2). ^1H NMR spectrum (DMSO-D_6): 5.55 (2 H, s, 2-CH_2), 8.13 (1 H, s, 3-H), 7.67 and 7.14 (4 H, dd, arom), 7.57...7.47 (5 H, m, arom), 4.12 (2 H, t, 5-CH_2), 3.83 (3 H, s, OCH_3), 2.95 (2 H, t, 8-CH_2), 2.17 (2 H, br.s, 6-CH_2), 1.98 ppm (2 H, s, 7-CH_2). IR spectrum: 3050, 2930 (C−H), 1650 cm^{-1} (C=N^+). Found, %: C 65.35, H 5.54, Br 18.77. Calc. for $C_{23}H_{23}BrN_2O$, %: C 65.25, H 5.48, Br 18.87.

2-(4′-Dimethylaminobenzylidene)-1-(4″-anisyl)-4-(4‴-chlorophenyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulenium Bromide (IVd). A mixture of salt IIIa (0.22 g, 0.48 mmol) and 4-dimethylaminobenzaldehyde (0.07 g, 0.48 mmol) was boiled in acetic anhydride (5 cm^3) for 5 min. After cooling, the mixture was treated with excess ether. The residue was filtered off and purified by recrystallization from propanol-2 to give the dye (0.2 g, 71%). M.p. 245-247°C. UV spectrum (ethanol): λ_{max} 511 nm (ε 34,000). Found, %: C 64.96, H 5.35, N 7.18. Calc. for $C_{32}H_{31}BrClN_3O$, %: C 65.26, H 5.31, N 7.13.

1-(4′-Anisyl)-2-acetyl-4-(4″-chlorophenyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta-[*c*,*d*]azulene (IIIe). A mixture of IIIa (0.38 g, 1 mmol), anhydrous sodium acetate (0.1 g, 1.2 mmol), and acetic anhydride (5 cm^3, 53 mmol) was heated to boiling and cooled. Acetic anhydride was removed in vacuum and water (50 cm^3) was added to the residue. After trituration, the crystals formed were filtered off, washed with water, dried and purified by recrystallization from benzene. Yield 0.36 g (86%). M.p. 243-244°C. ^1H NMR spectrum ($CDCl_3$): 1.90 (3 H, s, $COCH_3$), 8.17 (1 H, s, 3-H), 7.45 and 7.41 (4 H, dd, arom), 7.21 and 6.97 (4 H, dd, arom), 3.93 (2 H, t, 5-CH_2), 3.87 (3 H, s, OCH_3), 2.53 (2 H, t, 8-CH_2), 2.08 (2 H, br.s, 6-CH_2), 1.94 ppm (2 H, s, 7-CH_2). IR spectrum: 3130, 2915, 2830 (C−H), 1600, 1560 cm^{-1}. Found, %: C 71.34, H 5.48, Cl 8.49, N 6.60. Calc. for $C_{25}H_{23}ClN_2O_2$, %: C 71.68, H 5.53, Cl 8.46, N 6.69.

2-Acetyl-1-(4′-bromophenyl)-4-(4″-anisyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene (IIIf) was obtained in 92% yield from base IIIb analogously to IIIe. M.p. 261-262°C. ^1H NMR spectrum (DMSO-D_6): 1.73 (3 H, s, $COCH_3$), 7.94 (1 H, s, 3-H), 7.65 and 7.30 (4 H, dd, arom), 7.53 and 7.05 (4 H, dd, arom), 3.93 (2 H, t, 5-CH_2), 3.82 (3 H, s, OCH_3), 2.40 (2 H, t, 8-CH_2), 2.05 (2 H, br.s, 6-CH_2), 1.87 ppm (2 H, s, 7-CH_2). IR spectrum: 3160, 2915, 2840 (C−H), 1605, 1570 cm^{-1}. Found, %: C 64.68, H 5.08, Br 16.98, N 6.15. Calc. for $C_{25}H_{23}BrN_2O_2$, %: C 64.8, H 5.00, Br 17.24, N 6.05.

2-Acetyl-1-phenyl-4-(4′-anisyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene (IIIg) was obtained in 76% yield from base IIIc analogously to IIIe. M.p. 214-215°C. ^1H NMR spectrum (DMSO-D_6): 1.70 (3 H, s, $COCH_3$), 7.94 (1 H, s, 3-H), 7.52 and 7.35 (4 H, dd, arom), 7.45...7.33 (5 H, m, arom), 3.93 (2 H, t, 5-CH_2), 3.82 (3 H, s, OCH_3), 2.40 (2 H, t, 8-CH_2), 2.01 (2 H, br.s, 6-CH_2), 1.85 ppm (2 H, s, 7-CH_2). IR spectrum: 2900, 2830 (C−H), 1595, 1570 cm^{-1}. Found, %: C 78.03, H 6.21, N 7.32. Calc. for $C_{25}H_{24}N_2O_2$, %: C 78.1, H 6.29, N 7.29.

1-(4′-Anisyl)-4-(4″-chlorophenyl)-2-formyl-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene (IIIh). Phosphorus oxychloride (0.2 cm^3, 2.1 mmol) was added with stirring and ice cooling to DMF (5 cm^3, 64 mmol). After the reagent had been stirred for 15 min at room temperature, IIIa (0.38 g, 1 mmol) was added. The mixture was heated on a water bath at 60°C for 1 h, cooled and poured into 10% alkali solution. The precipitate was filtered off washed with water, dried and purified by recrystallization from chloroform−propanol-2 (1:1). Yield 0.23 g (56%). M.p. 233-235°C. ^1H NMR spectrum (DMSO-D_6): 9.03 (1 H, s, COH), 7.99 (1 H, s, 3-H), 7.63 and 7.58 (4 H, dd, arom), 7.39 and 6.99 (4 H, dd, arom), 3.98 (2 H, t, 5-CH_2), 3.79 (3 H, s, OCH_3), 2.56 (2 H, t, 8-CH_2), 2.12 (2 H, br.s, 6-CH_2), 1.97 ppm (2 H, s, 7-CH_2). IR spectrum: 2930, 2830 (C−H), 1610, 1500 cm^{-1}. Found, %: C 71.12, H 5.28, Cl 8.48, N 7.06. Calc. for $C_{24}H_{21}ClN_2O_2$, %: C 71.26, H 5.24, Cl 8.65, N 6.93.

N-Methylamide of 1-(4′-anisyl)-4-(4″-chlorophenyl)-5,6,7,8-Tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene-2-carboxylic Acid (IIIi). Methyl isocyanate (0.1 cm^3, 1.6 mmol) was added to a solution of base IIIa (0.38 g, 1 mmol) in benzene (10 cm^3). The reaction mixture was kept at 32°C for 2 h and the solvent was then removed in vacuum. The residue was purified by recrystallization from chloroform−propanol-2 (1:1), Yield 0.3 g (68%). M.p. 227-228°C. ^1H NMR spectrum (DMSO-D_6): 5.31 (1 H, q, NH), 2.59 (3 H, d, NCH_3), 7.85 (1 H, s, 3-H), 7.59 and 7.58 (4 H, dd, arom), 7.30 and 7.00

(4 H, dd, arom), 3.87 (2 H, br.s, 5-CH_2), 3.81 (3 H, s, OCH_3), 2.45 (2 H, t, 8-CH_2), 2.00 (2 H, br.s, 6-CH_2), 1.84 ppm (2 H, s, 7-CH_2). IR spectrum : 3440 (N−H), 2920, (C−H), 1620, 1560 cm^{-1}. Found, %: C 69.05, H 5.50, Cl 8.27, N 9.56. Calc. for $C_{25}H_{24}ClN_3O_2$, %: C 69.2, H 5.57, Cl 8.17, N 9.68.

N-Methylamide of 1-(4′-bromophenyl)-4-(4″-anisyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene-2-carboxylic acid (IIIj) was prepared in 86% yield analogously to IIIi from base IIIb. M.p. 240-241°C (from propanol-2). ^1H NMR spectrum (DMSO-D_6): 5.55 (1 H, q, NH), 2.58 (3 H, d, NCH_3), 7.71 (1 H, s, 3-H), 7.65 and 7.28 (4 H, dd, arom), 7.49 and 7.04 (4 H, dd, arom), 3.85 (2 H, br.s, 5-CH_2), 3.80 (3 H, s, OCH_3), 2.43 (2 H, t, 8-CH_2), 1.97 (2 H, br.s, 6-CH_2), 1.81 ppm (2 H, s, 7-CH_2). IR spectrum: 3440 (N−H), 2920, (C−H), 1610, 1560 cm^{-1}. Found, %: C 62.57, H 5.11, Br 16.59, N 8.86. Calc. for $C_{25}H_{24}BrN_3O_2$, %: C 62.77, H 5.06, Br 16.7, N 8.78.

N-(α,α,α-Trifluoro-3′-tolyl)thioamide of 1-(4″-anisyl)-4-(4‴-chlorophenyl)-5,6,7,8-Tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene-2-carboxylic acid (IIIk). A mixture of base IIIa (0.38 g, 1 mmol), 3-trifluoromethylphenyl isothiocyanate (0.2 g, 1 mmol) and benzene (25 cm^3) was boiled for 1 h. After cooling, the precipitate was filtered off and was purified by recrystallization from benzene. Yield 0.5 g (85%). M.p. 229-230°C. ^1H NMR Spectrum ($CDCl_3$): 9.13 (1 H, s, NH), 8.25 (1 H, s, 3-H), 7.91...7.05 (12 H, m, arom), 3.96 (2 H, br.s, 5-CH_2), 3.88 (3 H, s, OCH_3), 2.53 (2 H, t, 8-CH_2), 2.10 (2 H, br.s, 6-CH_2), 1.96 ppm (2 H, s, 7-CH_2). IR spectrum: 3350 (N−H), 2930, 2840 (C−H), 1320 cm^{-1}. Found, %: C 64.03, H 4.40, N 7.31. Calc. for $C_{31}H_{25}ClF_3N_3OS$, %: C 64.23, H 4.35, N 7.25.

N-(α,α,α-Trifluoro-3′-tolyl)thioamide of 1-phenyl-4-(4″-anisyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclo-penta[*c*,*d*]-azulene-2-carboxylic acid (IIIl) was obtained in 76% yield from base IIIc analogously to IIIk. M.p. 212-213°C (from chloroform−propanol-2 (1:2)). ^1H NMR spectrum ($CDCl_3$): 9.08 (1 H, s, NH), 8.04 (1 H, s, 3-H), 7.72...6.99 (13 H, m, arom), 3.94 (2 H, br.s, 5-CH_2), 3.88 (3 H, s, OCH_3), 2.54 (2 H, t, 8-CH_2), 2.08 (2 H, br.s, 6-CH_2), 1.96 ppm (2 H, s, 7-CH_2). IR spectrum: 3370 (N−H), 2930, 2850 (C−H), 1335 cm^{-1}. Found, %: C 68.02, H 4.88, N 7.82, S 5.93. Calc. for $C_{31}H_{26}F_3N_3OS$, %: C 68.24, H 4.80, N 7.70, S 5.88.

2-Nitroso-1-(4′-anisyl)-4-(4″-chlorophenyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene (IIIm). Amyl nitrite (0.2 cm^3) was added with stirring to a solution of base IIIa (0.23 g, 0.6 mmol) in benzene. After 2 h at room temperature the precipitate was filtered off and purified by recrystallization from chloroform−propanol-2 (1:1). Yield 0.21 g (85%). M.p. 213-215°C. ^1H NMR spectrum ($CDCl_3$): 8.36 (1 H, s, 3-H), 7.66 and 6.86 (4 H, dd, arom), 7.37 and 7.23 (4 H, dd, arom), 3.96 (2 H, br.s, 5-CH_2), 3.84 (3 H, s, OCH_3), 2.87 (2 H, t, 8-CH_2), 2.18 (2 H, br.s, 6-CH_2), 2.02 ppm (2 H, s, 7-CH_2). IR spectrum: 1476 cm^{-1} (C−N=O). Found, %: C 67.86, H 4.92, N 10.42, Cl 8.80. Calc. for $C_{23}H_{20}ClN_3O_2$, %: C 68.06, H 4.97, N 10.35, Cl 8.73.

2-Nitroso-1-phenyl-4-(4′-anisyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*c*,*d*]azulene (IIIn) was prepared in 92% yield from base IIIc analogously to IIIm. M.p. 185-186°C (from propanol-2). ^1H NMR spectrum ($CDCl_3$): 8.41 (1 H, s, 3-H), 7.77 and 6.96 (4 H, dd, arom), 7.45...7.27 (5 H, m, arom), 3.99 (2 H, t, 5-CH_2), 3.86 (3 H, s, OCH_3), 2.91 (2 H, t, 8-CH_2), 2.18 (2 H, br.s, 6-CH_2), 2.02 ppm (2 H, s, 7-CH_2). IR spectrum: 1474 cm^{-1} (C−N=O). Found, %: C 74.21, H 5.66, N 11.41. Calc. for $C_{23}H_{21}N_3O_2$, %: C 74.36, H 5.70, N 11.32.

REFERENCES

1. V. A. Kovtunenko, K. G. Nazarenko, and A. M. Demchenko, Tetrahedron, **52**, 9835 (1996).
2. A. A. Druzhimina, P. M. Kochergin, and L. M. Alekseeva, Khim. Geterotsikl. Soedin., No. 4, 405 (1972).
3. AMI and CNDO Programs from the GyperChem Suite, Version 4.0. Hypercube Inc. (1994).
4. J. Emsley, J. Finney, and L. Sutcliffe, High Resolution NMR Spectroscopy [Russian translation], Vol. 2, Mir, Moscow (1968).
5. F. S. Babichev and V. A. Kovtunenko, Ukr. Khim. Zh., **41**, 181 (1975).
6. F. S. Babichev, G. P. Kutrov, and M. Yu. Kornilov, Ukr. Khim. Zh., **34**, 1020 (1968).