SYNTHESIS AND STRUCTURES OF 10-HYDROXY- AND 10-ACETOXY-6(5H)PHENANTHRIDINONES

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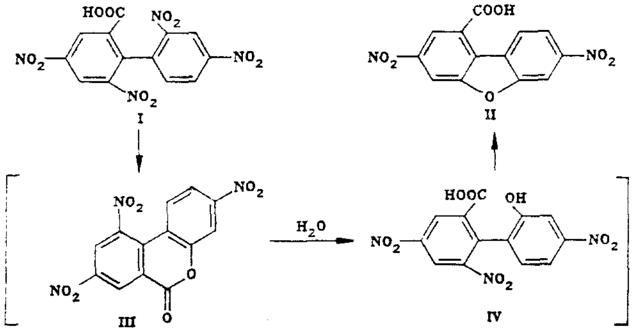
UDC 547.836.3:548.737

Treatment of 2,4,8,10-tetranitro-6(5H)-phenanthridinone with hexamethylphosphoric triamide leads to intermolecular nucleophilic substitution of the nitro group by a hydroxy group, the source of which is the water contained in the solvent, to give 10-hydroxy-2,4,8-trinitro-6(5H)-phenanthridinone. An intramolecular interaction with the participation of a proton of the aromatic ring and an oxygen atom of the hydroxy or acetoxy group of the 10-hydroxy- or 10-acetoxy-2,4,8,-trinitro-6(5H)-phenanthridinone, the properties of which are characteristic for an intramolecular hydrogen bond, was detected by x-ray diffraction analysis and PMR spectroscopy.

The ability of the nitro groups in polynitro compounds to be easily replaced by nucleophilic particles can be used to create new substances with predesignated properties and, depending on the structure of the starting molecule, to construct heterocycles. The latter possibility is of particular interest in the development of new preparative methods of synthesis. We developed one such method in a study of the action of strong, polar, aprotic solvents on nitro-substituted 2-carboxybiphenyls. It was shown that the successive replacement of two o-nitro groups with the formation of 1-carboxy-3,7-dinitrodibenzofuran (II) occurs when 2',4,4',6-tetranitro-2-carboxybiphenyl (I) is heated in dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) [1]. The initial step is probably intramolecular nucleophilic substitution of the o-nitro group by the carboxylate anion with the formation of 3,8,10-trinitro-6H-dibenzo[b,d]pyran-6-one (III), which, through the addition of a molecule of water, opens up to give 2'-hydroxy-4,4',6-trinitro-2-carboxybiphenyl (IV). A second o-nitro group is then replaced by the hydroxy group to give II.



Compound III, which was obtained independently, also undergoes cyclization to dibenzofuran II when it is heated in DMSO [2], evidently through the intermediate formation of hydroxy acid IV. One might have assumed that heteroanalogs of III containing nitro groups, one of which is in the ortho position relative to the bond that connects the two benzene rings, would undergo this sort of transformation. A convenient subject of investigation to verify this assumption is 2,4,8,10-tetranitro-6(5H)-phenanthridinone (V).

Scientific-Research Institute of Organic Intermediates and Dyes, Moscow 103787. L. Ya. Karpov Scientific-Research Institute of Physical Chemistry, Moscow 107120. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 314-319, March, 1987. Original article submitted November 14, 1985.

0009-3122/87/2303-0261$12.50

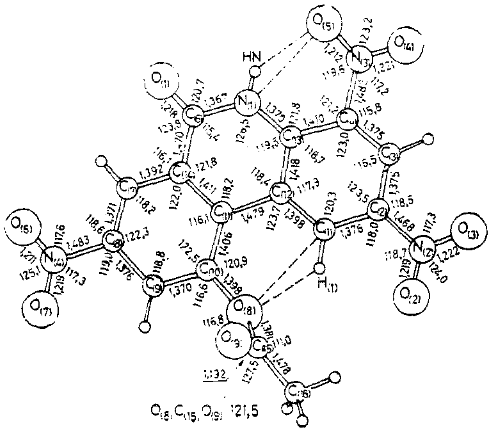


Fig. 1. Bond lengths (Å) and bond angles (deg) in the 10-acetoxy-2,4,8-trinitro-6(5H)-phenanthridinone (IX) molecule (the H bonds are denoted by dashed lines).

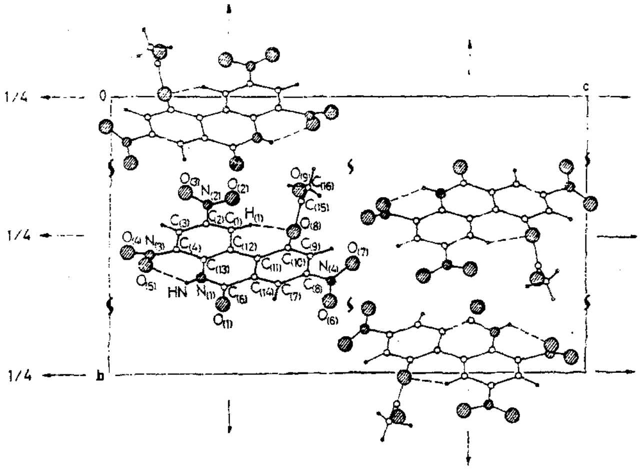
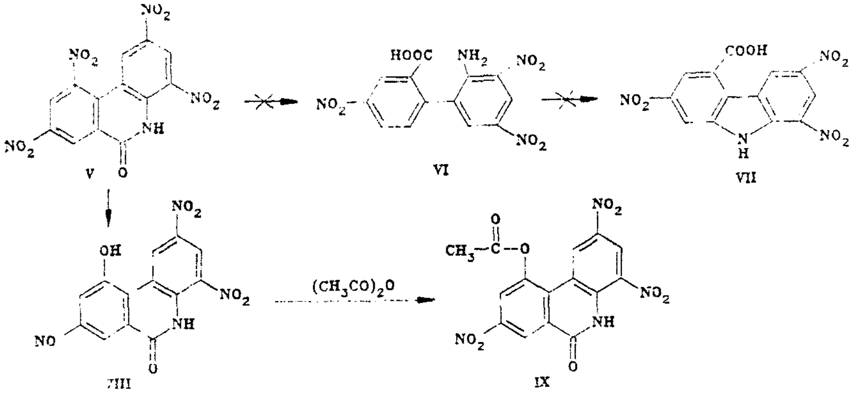


Fig. 2. Packing of 10-acetoxy-2,4,8-trinitro-6(5H)-phenanthridinone (IX) molecules in the crystal.

Cleavage of the lactam fragment with subsequent intramolecular nucleophilic substitution of the o-nitro group by the amino group of amino acid VI, which would result in the formation of 1-carboxy-3,6,8-trinitrocarbazole (VII), could occur when lactam V is heated in DMSO or DMF. However, V proved to be resistant to the action of DMSO and DMF even in the case of refluxing. Intermolecular nucleophilic substitution of the nitro group by a hydroxy group with the formation of 10-hydroxy-2,4,8-trinitro-6(5H)-phenanthridinone (VIII) occurs when V is heated in a stronger, polar, aprotic solvent, viz., hexamethylphosphoric triamide. The active attacking particle evidently is either a hydroxide ion formed under the reaction conditions from the water contained in the solvent through detachment of a proton by hexamethylphosphoric triamide or a complex of water with hexamethylphosphoric triamide, which forms an associated ion pair through protonation of a solvent molecule by water.

When a solution of V in hexamethylphosphoric triamide is refluxed, the reaction is complete after 2 h, as compared with 4 months when the solution is allowed to stand at 20°C. Compound VIII is formed in 70% yield. In DMSO and DMF replacement of a nitro group by a hydroxy group occurs only in the case of refluxing in the presence of an alkali.

According to the results of x-ray diffraction analysis of a single crystal of V [3], the nitro group in the 4 position is linked by an intramolecular hydrogen bond (IHB) with the hydrogen atom of the NH group; this is generally characteristic for nitro-substituted 6(5H)-phenanthridinones that contain a nitro group in the 4 position [4]. Another peculiarity of the structure of V is rotation of the nitro group in the 10 position relative to the plane of the benzene ring by 65.7° (the nitro groups in the 2, 4, and 8 positions have



angles of rotation of, respectively, 11.5°, 2.3°, and 23.5°). It is interesting to note that the nitro group that has the greatest angle of rotation undergoes nucleophilic substitution by the hydroxy group.

The position of the hydroxy group was proved on the basis of the results of x-ray diffraction analysis of 10-acetoxy-2,4,8-trinitro-6(5H)-phenanthridinone (IX), which was obtained by acetylation of lactam VIII with acetic anhydride, and data from the PMR spectra of VIII and IX.

The structure of the IX molecule is shown in Fig. 1. The standard deviations in the bond lengths and bond angles are, respectively, 0.004-0.005 Å and 0.3°. The molecule is stabilized by two $N_{(1)}—H_{(N)}...O_{(5)}$ and $C_{(1)}—H_{(1)}...O_{(8)}$ intramolecular hydrogen bonds. The geometrical parameters of the first H bond are as follows: $N_{(1)}—H_{(N)}$ 0.76(4) Å, $N_{(1)}...O_{(5)}$ 2.640(4) Å, $H_{(N)}...O_{(5)}$ 2.10(3) Å, $N_{(1)}H_{(N)}O_{(5)}$ 129(4)°. The same length of the NH...O intramolecular bond is found in N-(2-indandionyl)-N-methylacetamidine (2.64 Å) [5], but it is somewhat smaller (2.61-2.62 Å) in 2,4,8,10-tetranitrophenanthridone [3], 2,4-dinitroaniline [6], N-(n-butyl)-N'-[(p-chlorophenoxy)acetyl]urea [7], and benzaldehyde 2-nitrophenylhydrazone [8]. In the structures of organic compounds shortening of the distances between CH, CH_2, or CH_3 groups and the O atom both within the molecule and between molecules is explained by the formation of CH...O hydrogen bonds. The crystallographic evidence for the existence of this sort of bond, which was first presented in [9], is reflected most fully in a review [10]. The parameters of the CH...O intramolecular bond found in the IX molecule [$C_{(1)}—H_{(1)}$ 0.95(4) Å, $C_{(1)}...O_{(8)}$ 2.820(4) Å, $H_{(1)}...O_{(8)}$ 2.14(4) Å, $C_{(1)}H_{(1)}O_{(8)}$ 127(4)°] lie in the range of values for H...O distances (2.080-2.399 Å) and CHO angles (94.3-155.7°) [10]. The participation of a CH group of the benzene ring in a CH...O IHB was also noted in 4-(4-N,N-diethylaminophenylimino)-3-methyl-1-phenyl-2-pyrazolin-5-one (H...O 2.03 Å, C...O 2.95 Å, CHO 148° [11], N-(2-tosylaminobenzylidene)aniline (2.33 Å, 3.027 Å, 134°, respectively) [12], N-(2-tosylaminobenzylidene)-benzylamine (2.01 Å, 3.013 Å, 138°) [13], and other structures [10].

In the phenanthridone crystal the three-ring system of the molecule is planar within 0.05 Å [14, 15]. In the IX molecule the phenanthridone system is markedly deformed under the influence of the substituting groups with deviation Δ of the atoms from the mean molecular plane within the limits 0.105-0.111 Å. The dihedral angle between the external rings,

TABLE 1. Chemical Shifts of the Aromatic Protons in the PMR Spectra of Nitro-Substituted 6(5H)-Phenanthridinones V, VIII, and IX

Compound	Proton signals, δ, ppm (d_6-DMSO)			
	1-H	3-H	7-H	9-H
V	9,28	9,10	8,65	9,02
VIII	10,36	8,99	8,46	8,10
IX	10.34	8.97	8.42	8.11

TABLE 2. Coordinates of the Atoms and Equivalent Isotropic Temperature Factors ($Å^2 \cdot 10^3$) ($Å^2 \cdot 10^2$ for U_{iso} for the H atoms) of Sample IX

Atom	X	Y	Z	U_{iso}^{eq}	Atom	X	Y	Z	U_{iso}^{eq}
$O_{(1)}$	1,3612(5)	0,7447(2)	0,2335(1)	45(1)	$C_{(7)}$	1,2596(5)	0,6774(2)	0,3533(1)	35(1)
$O_{(2)}$	0,1847(4)	0,3737(2)	0,2578(1)	54(1)	$C_{(8)}$	1,2022(6)	0,6398(3)	0,4113(1)	35(1)
$O_{(3)}$	0,1943(5)	0,3515(2)	0,1585(1)	79(1)	$C_{(9)}$	1,0088(6)	0,5769(3)	0,4217(1)	38(1)
$O_{(4)}$	0,7134(5)	0,5615(3)	0,0362(1)	75(1)	$C_{(10)}$	0,8700(6)	0,5501(2)	0,3724(1)	34(1)
$O_{(5)}$	1,0451(5)	0,6038(2)	0,0736(1)	67(1)	$C_{(11)}$	0,9188(5)	0,5835(2)	0,3113(1)	31(1)
$O_{(6)}$	1,4932(5)	0,7392(3)	0,4582(1)	82(1)	$C_{(12)}$	0,7870(5)	0,5517(2)	0,2553(1)	29(1)
$O_{(7)}$	1,3470(6)	0,6050(2)	0,5094(1)	61(1)	$C_{(13)}$	0,8724(6)	0,5843(2)	0,1964(1)	32(1)
$O_{(8)}$	0,6701(4)	0,4903(2)	0,3859(1)	38(1)	$C_{(14)}$	1,1178(5)	0,6489(2)	0,3036(1)	30(1)
$O_{(9)}$	0,8858(4)	0,3394(2)	0,3969(1)	55(1)	$C_{(15)}$	0,7000(7)	0,3815(3)	0,3996(2)	40(1)
$N_{(1)}$	1,0628(5)	0,6507(2)	0,1932(1)	38(1)	$C_{(16)}$	0,4758(7)	0,3291(3)	0,4141(2)	60(1)
$N_{(2)}$	0,2718(5)	0,3886(2)	0,2069(1)	45(1)	$H_{(N)}$	1,107(7)	0,669(3)	0,162(2)	5(1)
$N_{(3)}$	0,8466(6)	0,5734(2)	0,0798(1)	48(1)	$H_{(1)}$	0,524(7)	0,466(3)	0,296(2)	5(1)
$N_{(4)}$	1,3607(5)	0,6635(3)	0,4638(1)	49(1)	$H_{(3)}$	0,492(8)	0,459(3)	0,105(2)	6(1)
$C_{(1)}$	0,5849(5)	0,4890(2)	0,2569(2)	34(1)	$H_{(7)}$	1,391(7)	0,725(3)	0,347(2)	5(1)
$C_{(2)}$	0,4802(6)	0,4567(3)	0,2025(2)	36(1)	$H_{(9)}$	0,960(7)	0,549(3)	0,465(2)	5(1)
$C_{(3)}$	0,5620(6)	0,4837(2)	0,1446(1)	39(1)	$H_{(16,1)}$	0,395(8)	0,362(4)	0,439(2)	7(2)
$C_{(4)}$	0,7577(6)	0,5474(3)	0,1426(2)	36(1)	$H_{(16,2)}$	0,493(9)	0,255(4)	0,429(2)	10(2)
$C_{(6)}$	1,1924(6)	0,6872(2)	0,2421(1)	35(1)	$H_{(16,3)}$	0,366(12)	0,321(5)	0,375(3)	15(3)

which are planar within 0.018 Å [the $C_{(1)}$—$C_{(4)}$, $C_{(12)}$, and $C_{(13)}$ atoms — plane 1] and 0.008 Å [the $C_{(7)}$—$C_{(11)}$ and $C_{(14)}$ atoms — plane 2], is 7.9°. The heteroring, which is planar within 0.025 Å, forms dihedral angles of 3.5° and 4.7° with planes 1 and 2, respectively. The $O_{(1)}$ atom is situated in the plane of the heteroring (Δ = 0.022 Å). In general, the three-ring system of the IX molecule with an acetoxy group in the 10 position is less deformed as compared with 2,4,8,10-tetranitrophenanthridone (V), for which the Δ values are 0.157-0.207 Å [3]. The angles of rotation of the nitro groups around the C—N bonds relative to plane 1 are 7.7° in the 2 position and 17.6° in the 4 position. In [3] the smaller angle of rotation of the NO_2 group in the 4 position (2.3°) leads to a stronger H bond. The nitro group in the 8 position is rotated 20.2° from plane 2, while the acetoxy group, which is planar within 0.018 Å [the $C_{(10)}$, $O_{(8)}$, $C_{(15)}$, $O_{(9)}$, and $C_{(16)}$ atoms], is rotated 75.9° (in [3] the angle of rotation of the NO_2 group in the 10 position is 65.7°). Tilting of the C—N (C—O) bonds to the planes of the benzene rings is also observed: Δ = 0.050 Å for $N_{(3)}$, Δ = 0.096 Å for $N_{(4)}$, and Δ = −0.075 Å for $O_{(8)}$. The geometry of the acetoxy group is close to that obtained in acetoxy derivatives of benzene [16].

The packing of the molecules in a projection on the crystallographic (100) plane is shown in Fig. 2 (IHB of two types are denoted by dashed lines). The molecules with an approximately planar principal fragment and an acetoxy group that deviates from it are situated in the crystal at an angle of 30° relative to the "a" axis and almost perpendicular (at an angle of ~84°) to the (001) plane. The intermolecular distances correspond to the normal van der Waals contacts, and the shortest of these are as follows: $O_{(1)}\ldots C_{(1)}$ 3.028(4) Å, $C_{(6)}\ldots C_{(1)}$ 3.342(4) Å, $C_{(6)}\ldots C_{(2)}$ 3.394 Å, and $O_{(4)}\ldots C_{(15)}$ 3.066(4) Å.

The existence of an IHB between the aromatic 1-H proton and the oxygen atom of the 10-hydroxy or 10-acetoxy group in VIII and IX was also established by means of the PMR spectra. The PMR spectra of VIII and IX are represented by four doublets of identical intensity. The assignments were made with the use of the principles of the effect of nitro groups on aromatic protons [17]. The spin—spin coupling constant (SSCC) of 2 Hz constitutes unambiguous evidence for substitution of the aromatic ring protons in the 2, 4, 8, and 10 positions. For the assignment of the signals these spectra were compared with the PMR spectrum of V (Table 1), as well as with data from an investigation of the effect on the chemical shifts of aromatic protons of replacement of the hydrogen atoms by methoxy groups in various positions of the benzene rings of 6(5H)-phenanthridinone [18].

The 0.9-ppm shift to strong field of the chemical shift of the 9-H proton in VIII and IX as compared with the position of this signal in the spectrum of tetranitrophenanthridone V shows that the hydroxy or acetoxy group in the investigated substances is in the 10 position. The significant shift (1.1 ppm) to weak field of the chemical shift of the 1-H proton can be due only to the formation of an IHB between the oxygen atom of the OH or OAc group in the 10 position and the 1-H proton. The indicated IHB in VIII and IX is evidently formed because of the presence of nitro groups in the 2 and 4 positions, which increase the acidity of the 1-H proton.

EXPERIMENTAL

The IR spectra of KCl pellets of the compounds were recorded with a Perkin-Elmer spectrometer. The PMR spectra of saturated solutions of the nitrophenanthridinones in d_6-DMSO (containing 99.3% of the isotope) were obtained with a Bruker HX-90 spectrometer under pulse-accumulation conditions at 100°C [with tetramethylsilane (TMS) as the internal standard]. The accuracy in the measurement of the chemical shifts was ±0.01 ppm. The purity of the products was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in an acetone–benzene system (1:10). The x-ray diffraction experiment was carried out with a Syntex P1 diffractometer. The light-yellow single crystals of IX, which were grown from a solution in acetic acid, were rhombic and had the following parameters: a = 5.7684(7), b = 12.300(2), c = 21.531(3) Å, v = 1527.6(4) Å^3, m = 388.3 ($C_{15}H_8N_4O_9$), space group $P2_12_12_1$, z = 4, and d_{calc} = 1.688 g/cm^3. The intensities of 1129 reflections with $I \geq 3\sigma(1)$ were used to decode the structure by the direct method and refinement up to an R factor of 0.028 (with allowance for all of the H atoms). The coordinates of the atoms and their equivalent isotropic temperature factors are presented in Table 2. All of the calculations were made by means of a set of SHELXTL and XTL programs in the Nicolet-R3 system.

10-Hydroxy-2,4,8-trinitro-6(5H)-phenanthridinone (VIII). A) A 7.5 g (0.02 mole) sample of V was added to 100 ml of hexamethylphosphoric triamide, after which the mixture was refluxed for 2 h, cooled, and poured into 400 ml of 3% HCl. The precipitate was removed by filtration and recrystallized from acetic acid to give 4.84 g (70%) of pale-yellow crystals with mp 193-194°C and R_f 0.36. IR spectrum: 3240, 3100, 2940, 1700 (C=O), 1620, 1605, 1545 (NO_2), 1460, 1435, 1345 (NO_2), 1305, 1195, 1130, 995, 800, 755 cm^{-1}. Found, %: C 45.0, H 1.7, N 16.2. $C_{13}H_6N_4O_8$. Calculated, %: C 45.1, H 1.7, N 16.2.

B) A 7.5-g (0.02 mole) sample of V was added to a mixture of 100 ml of DMSO and 10 g of finely ground potassium hydroxide powder, after which the mixture was refluxed for 4 h, cooled, and poured into a mixture of 300 g of ice and 30 ml of concentrated HCl. The precipitate was removed by filtration, washed with water, dried, and recrystallized from acetic acid to give 4.5 g (65%) of VIII, which was identical to a sample from the preceding experiment.

C) A mixture of DMF, potassium hydroxide, and V was refluxed as described in method B to give VIII (68%), which was identical to the samples obtained by methods A and B.

10-Acetoxy-2,4,8-trinitro-6(5H)-phenanthridinone (IX). A 3.46-g (0.01 mole) sample of VIII was added to 50 ml of acetic anhydride, after which the mixture was refluxed for 1 h, cooled to 20°C, and poured over 250 g of ice. The precipitate was removed by filtration, washed with water, and dried to give 3.69 g (95%) of light-yellow crystals with mp 217-218°C (from acetic acid) and R_f 0.59. IR spectrum: 3330, 3100, 1790 (C=O), 1700 (C=O), 1630, 1560 (NO_2), 1490, 1440, 1360 (NO_2), 1340, 1310, 1235, 1185, 1030, 930, 865, 840, 805, 770, 740 cm^{-1}. Found, %: C 46.3, H 2.1, N 14.5. $C_{15}H_8N_4O_9$. Calculated, %: C 46.3, H 2.1, N 14.4.

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SYNTHESIS OF AMINO-SUBSTITUTED 2-METHYLCOUMARINS, CHROMANS, AND BENZOXEPANES AND THEIR N-(ALKYLAMINOACYL) DERIVATIVES

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UDC 547.728'814'89:543.422.
25:542.941'944'958.1'3

The isomeric compositions of the products of nitration of 2-methylcoumaran and chroman with acetyl nitrate were determined. More convenient methods for the synthesis of 7-amino-2-methylcoumaran and 8-aminochroman were developed, and 9-amino-1-benzoxepane was obtained for the first time. Alkylaminoacylamino-substituted 2-methylcoumarans, chromans, and 1-benzoxepanes were synthesized. A method for the synthesis of 2-bromocaproyl chloride from caproic acid was developed.

Amino-substituted coumarans, chromans, and benzoxepanes are of interest for the synthesis of physiologically active substances [1-4]; however, convenient methods for obtaining many amines of this type are not available. Thus 7-amino-2-methylcoumaran (IIb) was obtained by catalytic hydrogenation of its benzofuran analog by heating under pressure [3, 4], and 8-aminochroman (IVb) was synthesized by a multistep method [5]. We have developed simpler methods for obtaining amines IIb and IVb, which consist in the nitration of 2-methylcoumaran and chroman with acetyl nitrate with subsequent reduction of the resulting mixtures of nitro derivatives Ia and IIa (in a ratio of 3:2) and, respectively, IIIa with IVa (in a ratio of 1:3) and chromatographic separation on silica gel of the resulting mixtures of amines Ib with IIb and IIIb with IVb into individual compounds. In the nitration with a mixture of nitric and acetic acids 2-methylcoumaran forms virtually only one nitro derivative (Ia), while chroman forms a mixture of isomers IIIa and IVa in a ratio of 4:1 [6]. The tendency of acetyl nitrate to nitrate an aromatic ring in the ortho position relative to a substituent that contains an unshared pair of electrons is well known [7]. Under the conditions that we used 1-benzoxepane is not nitrated by acetyl nitrate, but amino derivatives Vb and VIb were obtained by the pathway indicated above from the mixture of its nitro derivatives Va with VIa (in a ratio of 2:1) formed by nitration with 70% nitric acid [6].

The possibility of the formation by isomers IIb, IVb, and VIb of an intramolecular hydrogen bond with the participation of the oxygen atom of the heteroring, which decreases their ability to be adsorbed on silica gel [8], assists in the chromatographic separation of mixtures of amines Ib with IIb, IIIb with IVb, and Vb with VIb.

V. Kapsukas Vilnius State University, Vilnius 232734. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 320-324, March, 1987. Original article submitted October 26, 1985.

0009-3122/87/2303-0266$12.50