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Carbenium Ions in Substitution Reactions at the Amino Nitrogen Atom

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Abstract—Tropylium, xanthylium, and tritylium salts characterized by different stabilities differently reacted with biologically active amines. The reactions of tropylium perchlorate and tetrafluoroborate with 4-(cyclohepta-2,4,6-trien-1-yl)aniline was accompanied by hydrolysis of the *N*-(cyclohepta-2,4,6-trien-1-yl) derivative, the *N*-xanthenyl derivative underwent dehydrogenation, whereas tritylium perchlorate failed to react with 4-(cyclohepta-2,4,6-trien-1-yl)aniline. The reactions of pyrimidin-2-amine with tropylium, xanthylium, and tritylium salts afforded products of substitution of one hydrogen atom in the amino group with high yields. The *N*-substituted pyrimidin-2-amine derivatives were stable, and neither their dehydrogenation nor hydrolysis was observed.

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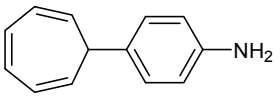
Nonbenzenoid aromatic systems such as tropylium and xanthylium cations, as well as tritylium salts, are convenient reagents for the introduction of 1,3,5-cycloheptatriene [1, 2], xanthene [3], or triphenylmethane fragments [4] into organic molecules. We previously synthesized 4-(cyclohepta-2,4,6-trien-1-yl)aniline (**1**) by reaction of tropylium perchlorate with aniline, its structure was determined by X-ray analysis, and its antimicrobial activity was studied [5–7]. The chemical properties of compound **1** have been poorly explored. Interest in the chemical behavior of amine **1** is related to its ability to inhibit the growth of the yeast-like fungus *C. albicans* and antibacterial activity against *S. aureus*. The use of tropylium salts to replace hydrogen in the amino group of **1** by 1,3,5-cycloheptatriene fragment in the presence of imidazole as an activator [2] allowed us to obtain *N*-[4-(cyclohepta-2,4,6-trien-1-yl)phenyl]cyclohepta-2,4,6-trien-1-amine (**2**) which showed a higher antimicrobial activity against *S. aureus* [6]. However, the reaction of tropylium perchlorate with 4-methoxyaniline under similar conditions afforded *N*-benzylidene-4-methoxyaniline instead of the expected *N*-cycloheptatrienyl derivative due to dehydrogenation and ring contraction processes [6].



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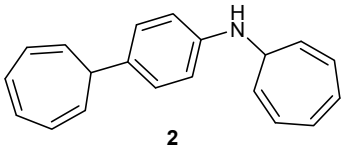

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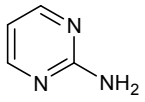

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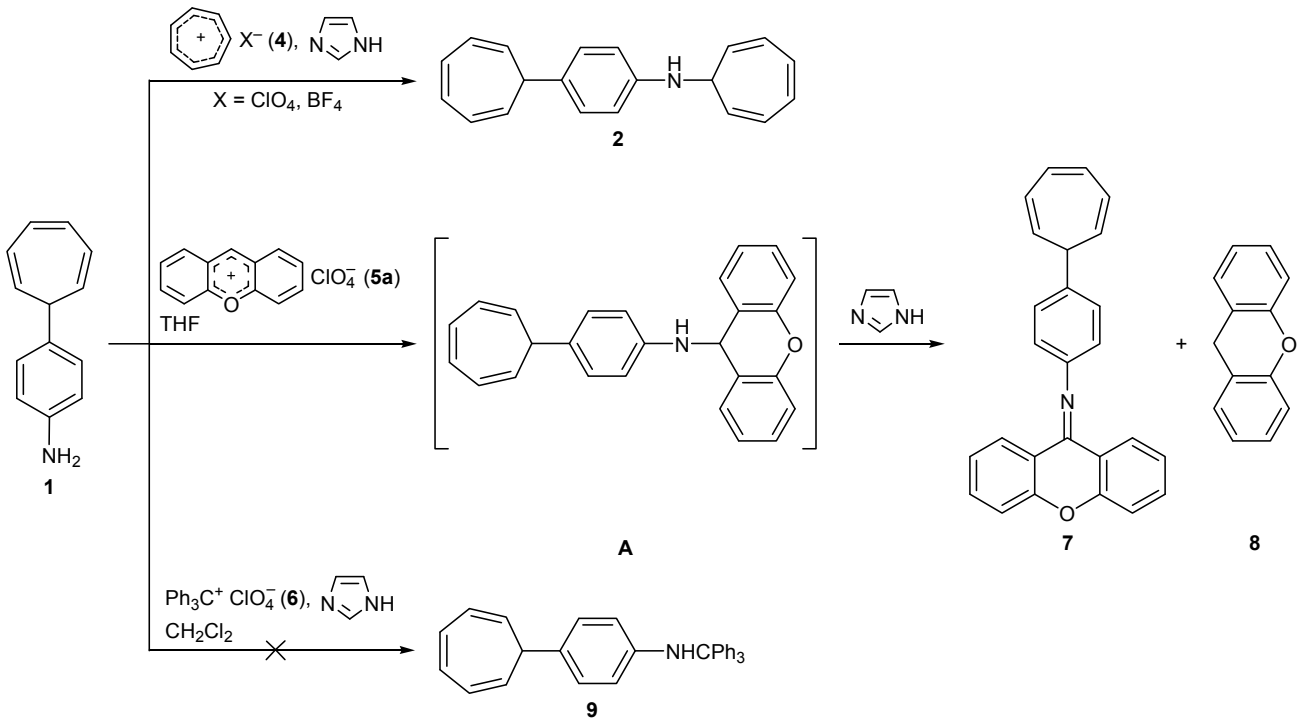
For further study of hydrogen substitution at the amino nitrogen atom we selected tropylium salts **4**, xanthylium salts **5a** and **5b**, and tritylium perchlorate **6**, which are characterized by considerably different stabilities (pK_R^+ 4.70, –0.84, and –6.63, respectively) [8]. The substrates were 4-(cyclohepta-2,4,6-trien-1-yl)aniline (**1**) and pyrimidin-2-amine (**3**) which is a known pharmacophore [9]. The reactivity of amine **3** toward salts **4**–**6** may depend on both the acidity of the NH hydrogen atom and related amine–imine tautomerism and orientating effect of the amino group (C^5 is an alternative site for electrophilic attack) [9–11].

The goal of the present work was to study reactions of amines **1** and **3** with tropylium, xanthylium, and tritylium salts and estimate the stability and yields of the products.

The results showed that, unlike amine **2** in which the cycloheptatriene ring remains unchanged during the synthesis and on storage [6], the reaction of **1** with xanthylium perchlorate (**5a**) in the presence of imidazole gave imine **7** as a result of dehydrogenation of initially formed *N*-xanthenyl derivative **A** (Scheme 1). The yield of **7** increased from 44 to 87% when 2 equiv

Scheme 1.

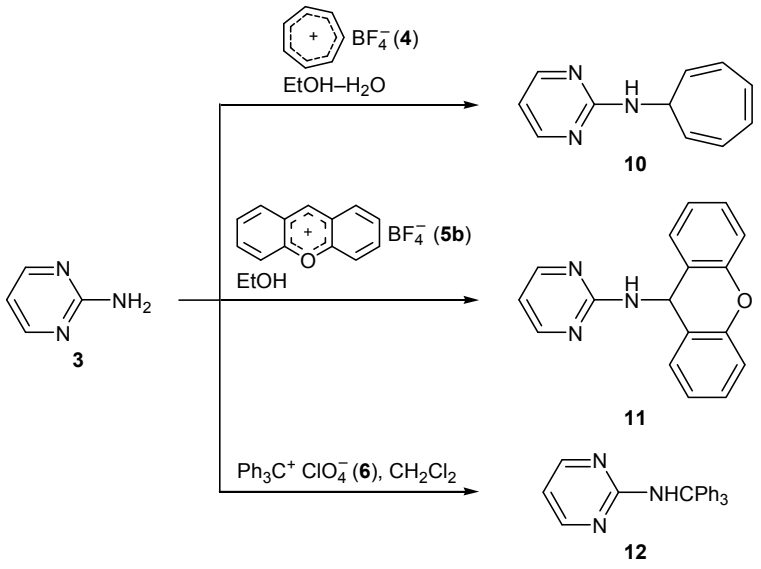


of **5a** was used; the second product was 9*H*-xanthene (**8**). The role of imidazole [2] or pyridine [12] in the reactions of amines with tropylium or xanthylium salts consists of generation of quaternary *N*-cycloheptatrienyl- or *N*-xanthenylammonium salts that are reactive electrophilic species favoring increased yield of the target product.

The stability of previously synthesized amine **2** containing two cycloheptatrienyl fragments was studied by special experiment. When a thin layer of **2** was kept for a month on exposure to air, it underwent complete hydrolysis with the formation of initial amine **1**; on the other hand, amine **2** is stable in the absence of atmospheric moisture.

The reaction of **1** with tritylium perchlorate (**6**) in the presence of imidazole gave no expected *N*-trityl-4-(cyclohepta-2,4,6-trien-1-yl)aniline **9**, which may be due to the low stability of salt **6**.

Scheme 2.



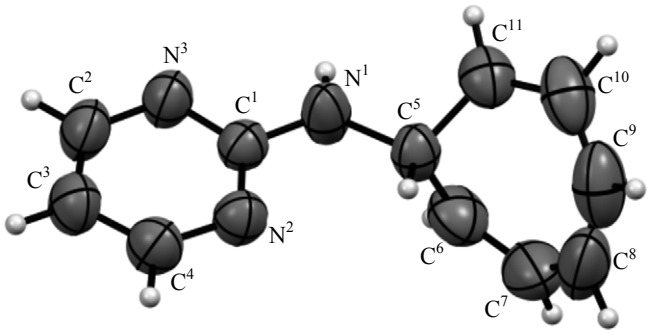


Fig. 1. Structure of the molecule of *N*-(cyclohepta-2,4,6-trien-1-yl)pyrimidin-2-amine (**10**) according to the X-ray diffraction data.

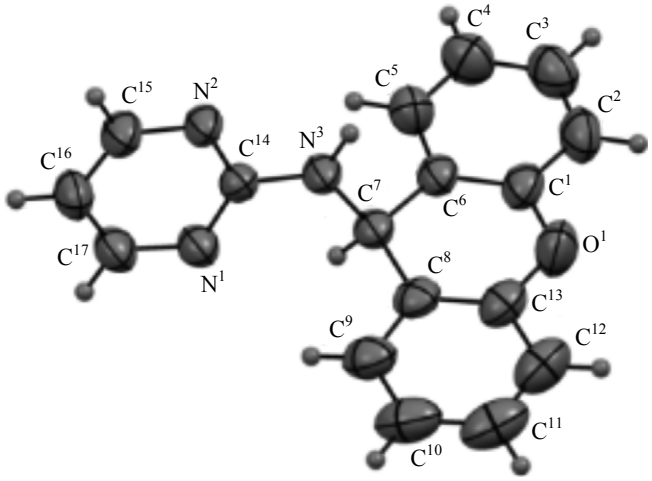


Fig. 2. Structure of the molecule of *N*-(9*H*-xanthen-9-yl)-pyrimidin-2-amine (**11**) according to the X-ray diffraction data.

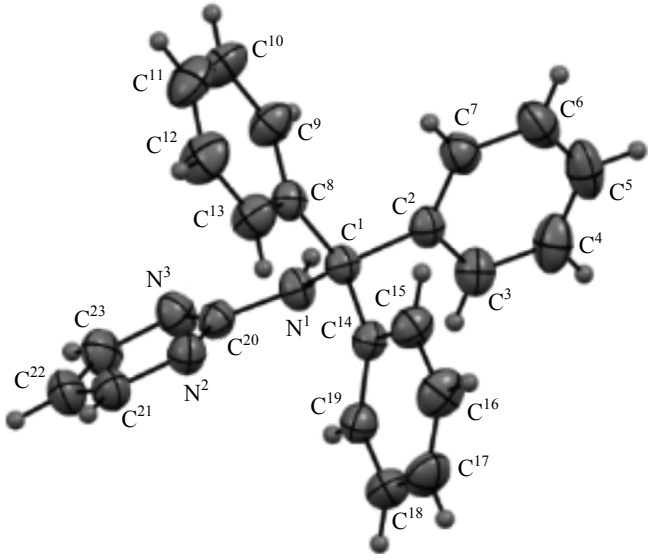


Fig. 3. Structure of the molecule of *N*-tritylpyrimidin-2-amine (**12**) according to the X-ray diffraction data.

The reactions of pyridin-2-amine (**3**) with salts **4**, **5b**, and **6** afforded the corresponding products of electrophilic substitution of one hydrogen atom on the amino group by cycloheptatriene, xanthene, or triphenylmethane fragment, respectively (Scheme 2). The products, amines **10**–**12** were stable, and their maximum yields were achieved using 2 equiv of salt **4**, **5b**, or **6**. Compounds **10**–**12** did not undergo dehydrogenation or hydrolysis during their synthesis, isolation, or storage, so that the introduced cycloheptatriene, xanthene, or triphenylmethane fragment was retained in their molecules. Thus, we have accomplished direct reactions of amine **3** with salts **4**, **5b**, and **6**, which involved exclusively the amino group rather than C^5 of the heteroring.

The structure of all isolated compounds was confirmed by ^{1}H NMR and mass spectra, as well as by X-ray analysis of amines **10**–**12**. According to the X-ray diffraction data (Figs. 1–3), the pyrimidine ring in molecules **10**–**12** is planar. The cycloheptatriene fragment in **10** adopts a *boat* conformation with equatorial orientation of the amino group. The xanthene fragment in **11** is planar within 0.043 Å, and it forms a diheral angle of 75.8° with the pyrimidine ring plane. The $C^1N^1C^7$ angle in molecule **12** is 124.0(2)°.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300 MHz using $CDCl_3$ as solvent and hexamethyldisiloxane as internal standard. The high-resolution mass spectra were recorded on a Bruker Daltonik maXis Impact HD instrument. The X-ray diffraction data for compound **10**–**12** were obtained with an Xcalibur R diffractometer. A correction for absorption was applied empirically by the multiscan method using SCALE3 ABSPACK algorithm [13]. The structures were solved by the direct method and were refined by the full-matrix least-squares method using SHELX 2013 software package [14].

***N*-[4-(Cyclohepta-2,4,6-trien-1-yl)phenyl]-9*H*-xanthen-9-imine (7).** *a.* A solution of 0.14 g (2 mmol) of imidazole in 8 mL of THF was cooled to 0°C, 0.28 g (1 mmol) of salt **5a** was added with stirring, and 0.18 g (1 mmol) of amine **1** was then added. The yellow mixture was stirred for 2.5 h at room temperature and neutralized to pH 8 with 10% aqueous ammonia. An oily material separated and crystallized in 24 h. It was filtered off, dried, treated with hexane to remove 9*H*-xanthene (**8**), and washed with acetone. Yield 0.16 g (44%), mp 148°C (from acetone).

b. A solution of 0.09 g (0.65 mmol) of imidazole in 7 mL of THF was cooled to 0°C, 0.37 g (1.31 mmol) of salt **5a** was added, and 0.12 g (0.65 mmol) of amine **1** was then added with stirring. The subsequent procedure was the same as in *a*. Yield 0.21 g (87%). ^{1}H NMR spectrum, δ, ppm: 2.57 t (1H, 7-H, J = 5.4 Hz), 5.23–5.31 m (2H, 1-H, 6-H), 6.18–6.23 m (2H, 2-H, 5-H), 6.69–6.71 m (2H, 3-H, 4-H), 6.97–7.36 m (12H, H_{arom}). Found: m/z 362.1542 $[M + H]^+$. $C_{26}H_{19}NO$. Calculated: M + H 362.4110.

***N*-(Cyclohepta-2,4,6-trien-1-yl)pyrimidin-2-amine (10).** Amine **3**, 0.19 g (2 mmol), was added in one portion to a solution of 0.18 g (1 mmol) of salt **4** in 2 mL of water and 4 mL of ethanol. The transparent solution was kept for 1.5 h at room temperature and neutralized to pH 8 with 10% aqueous ammonia. Yield 0.17 g (92%), white crystals, mp 100–102°C (from hexane). ^{1}H NMR spectrum, δ, ppm: 3.89 br.s (1H, NH), 4.37–4.41 d.t (1H, 1-H, J = 4.54, 4.47 Hz), 5.56–5.60 m (2H, 2-H, 7-H), 6.30–6.34 m (2H, 3-H, 6-H), 6.61 t (1H, 5′-H, J = 7.32 Hz), 6.75–6.77 m (2H, 4-H, 5-H), 8.32 d (2H, 4′-H, 6′-H, J = 3.6 Hz). Found: m/z 186.1028 $[M + H]^+$. $C_{11}H_{12}N_3$. Calculated: M + H 186.1026.

Monoclinic crystal system, space group $P2_1/c$, $C_{11}H_{11}N_3$; unit cell parameters [295(2) K]: a = 9.701(3), b = 7.280(3), c = 14.350(4) Å; β = 92.83(3)°; V = 1012.2(6) Å^3; Z = 4. The structure was solved by the full-matrix least-squares method in anisotropic approximation for all non-hydrogen atoms. The NH hydrogen was localized from the difference electron density maps and was refined independently in isotropic approximation; the other hydrogen atoms were refined according to the riding model in isotropic approximation with dependent thermal parameters. Final divergence factors: R_1 = 0.0579, wR_2 = 0.1547 [1384 reflections with $I > \sigma(I)$]; R_1 = 0.0978, wR_2 = 0.1897 (2406 independent reflections); goodness of fit S = 1.033.

***N*-(9*H*-Xanthen-9-yl)pyrimidin-2-amine (11).** Salt **5b**, 0.13 g (0.5 mmol), was added in one portion to a solution of 0.09 g (1 mmol) of amine **3** in 5 mL of ethanol. After stirring, the mixture became homogeneous, and a solid precipitated in 10 min. After 1.5 h, the mixture was neutralized to pH 8 with 10% aqueous ammonia. Yield 0.09 g (66%), white crystals, mp 179–180°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.20 t (1H, NH, J = 4.6 Hz), 5.97 d (1H, 9′-H, J = 6.9 Hz), 6.62 t (1H, 5-H, J = 3.6 Hz), 7.07–7.16 m (4H, 2′-H, 3′-H, 6′-H, 7′-H), 7.34 m (2H, 1′-H, 8′-H), 7.53 d (2H, 4′-H, 5′-H, J = 5.5 Hz), 8.31 d (2H, 4-H, 6-H, J = 3.0 Hz). Found: m/z 276.1129 $[M + H]^+$. $C_{17}H_{13}N_3O$. Calculated: M + H 276.1131.

Triclinic crystal system, space group P-1, $C_{17}H_{13}N_3O$; unit cell parameters [295(2) K]: a = 8.5519(17), b = 9.0036(17), c = 10.2897(19) Å; α = 110.501(17), β = 108.397(17), γ = 95.156(16)°; V = 686.05(85) Å^3; Z = 2; d_{calc} = 1.33 g/cm^3; F(000) = 287.9; μ = 0.086 mm^{-1}. Total of 5151 reflection intensities were measured, including 3151 independent reflections (R_{int} = 0.0379) and 1948 reflections with $I > 2\sigma(I)$]. Final divergence factors: R_1 = 0.0581, wR_2 = 0.1459 [reflections with $I > 2\sigma(I)$]; R_1 = 0.0905, wR_2 = 0.1764 (all independent reflections); goodness of fit S = 1.020.

***N*-Tritylpyrimidin-2-amine (12).** Salt **6**, 0.83 g (2.5 mmol), was added in one portion to a solution of 0.24 g (2.5 mmol) of amine **3** in 10 mL of methylene chloride. The resulting solution was refluxed for 0.5 h and cooled, the solvent was completely removed, and the residue was treated with 10% aqueous ammonia to pH 8. The precipitate was filtered off and recrystallized. Yield 0.54 g (63%), white crystals, mp 168–169°C (from benzene). ^{1}H NMR spectrum spectrum, δ, ppm: 3.10 s (1H, NH), 6.41 t (1H, 5-H, J = 4.8 Hz), 7.18–7.34 m (15H, H_{arom}), 8.03 d (2H, 4-H, 6-H, J = 6.0 Hz). Found: m/z 338.1647 $[M + H]^+$. $C_{23}H_{19}N_3$. Calculated: M + H 338.1652.

Monoclinic crystals, space group $I2/a$, $C_{23}H_{19}N_3$; unit cell parameters [295.0(2) K]: a = 28.9764(46), b = 9.1914(14), c = 15.1479(25) Å; β = 95.983(15)°; V = 4012.42(64) Å^3; Z = 8; d_{calc} = 1.25 g/cm^3; F(000) = 1592; μ = 0.074 mm^{-1}. Total of 18937 reflection intensities were measured, including 4910 independent reflections (R_{int} = 0.0421) and 3409 reflections with $I > 2\sigma(I)$]. Final divergence factors: R_1 = 0.0716, wR_2 = 0.1999 [reflections with $I > 2\sigma(I)$]; R_1 = 0.1005, wR_2 = 0.2156 (all independent reflections); S = 1.072.

The CIF files containing complete sets of crystallographic data for compounds **10**–**12** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry nos. 1832665, 1832664, and 1832663, respectively) and are available at *www.ccdc.cam.ac.uk/data_request/cif*.

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