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Synthesis of Some Naphthyl-Substituted Nitrogen Heterocycles on the Basis of (*Z*)-3-Chloro-3-(2-naphthyl)propenal

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Abstract—β-Naphthyl-substituted derivatives of pyrazole, benzodiazepine, isoxazole, and pyrimidine were synthesized by reactions of (*Z*)-3-chloro-3-(2-naphthyl)propenal with hydrazine, *o*-phenylenediamine, hydroxylamine, and formamide, respectively.

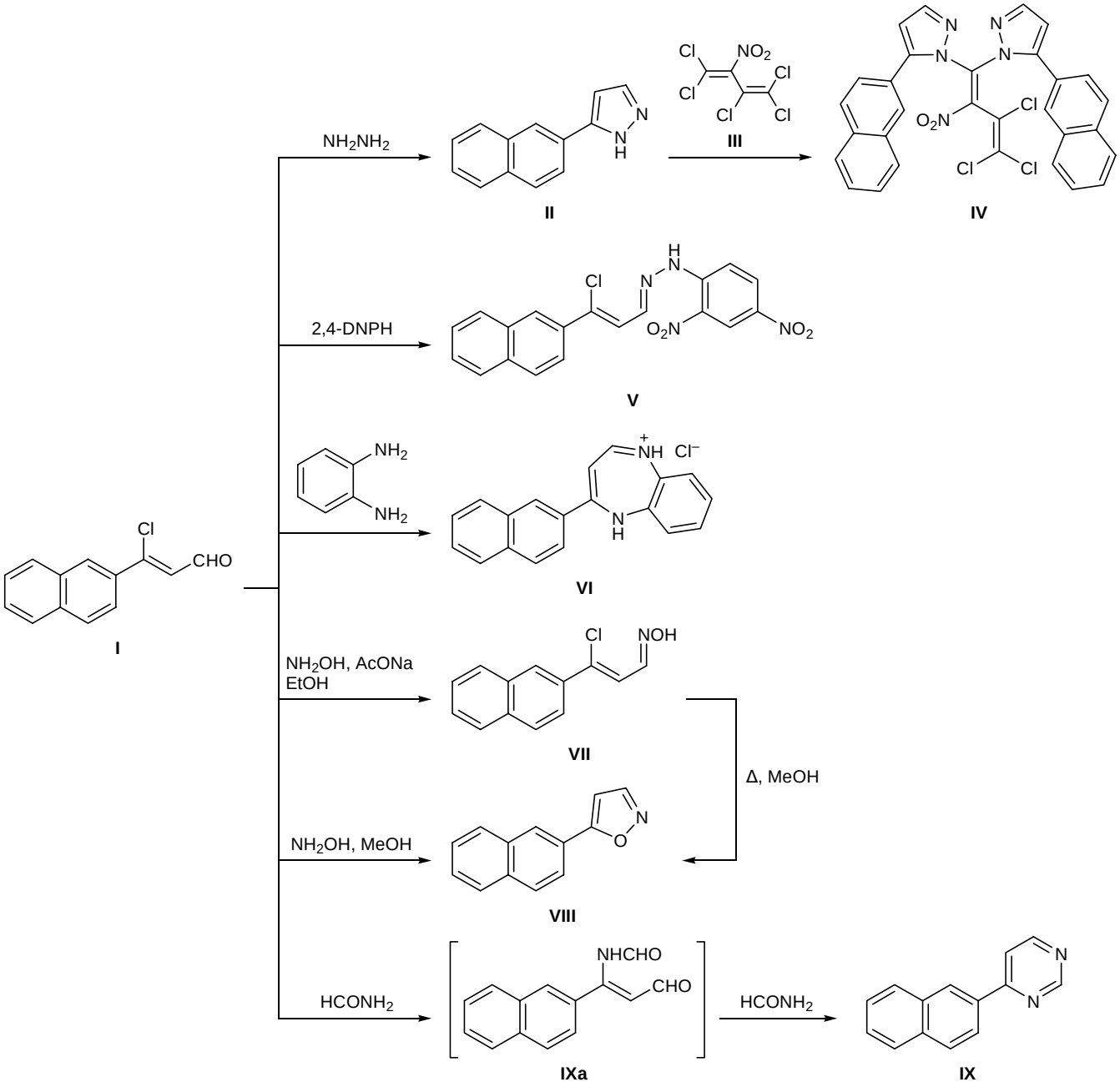
(*Z*)-3-Chloro-3-(2-naphthyl)propenal (**I**), which is readily available from 2-acetylnaphthalene via Vilsmeier–Haack reaction [1], is a reactive synthon for the preparation of various organic compounds containing a naphthalene fragment. The chlorine atom at the C=C bond in molecule **I** is activated due to conjugation with the electron-acceptor carbonyl group, and it can readily be replaced by other functional groups. The presence in molecule **I** of two reactive centers (C=O and =C–Cl) makes it possible to build up various heterocyclic systems. We recently showed that (*Z*)-3-chloro-3-(2-naphthyl)propenal readily reacts with primary aromatic amines to give naphthylimino enamines which undergo intramolecular cyclization to naphthyl-substituted quinolines [2]. The goal of the present study was to develop methods of synthesis of various nitrogen-containing heterocycles by reactions of (*Z*)-3-chloro-3-(2-naphthyl)propenal (**I**) with a series of nucleophiles. As the latter we used hydrazine, 2,4-dinitrophenylhydrazine, *o*-phenylenediamine, hydroxylamine, and formamide.

It is known [3] that the reaction of β-chlorovinyl ketones with hydrazine underlies a preparative procedure for the synthesis of pyrazole derivatives. We expected that analogous reaction of chloropropenal **I** should also lead to formation of the corresponding naphthyl-substituted heterocycle. In fact, aldehyde **I** reacted with hydrazine hydrate to afford 74% of 5-(2-naphthyl)pyrazole (**II**) which was identified on the basis of its spectral data and elemental composition. The ^{13}C NMR spectrum of pyrazole **II** was reported in [4]; however, neither procedure for preparation of this compound nor its other spectral data were given (although the authors noted that this compound was previously unknown). The molecule of naphthylpyrazole **II** contains an N-nucleophilic center (NH); therefore, we examined its alkylation with 2-nitropentachloro-1,3-butadiene (**III**) which is known as a highly reactive electrophilic agent toward various amines [5]. The reaction involved replacement of both geminal chlorine atoms in the dichloronitrovinyl fragment of **III** and resulted in formation of a bis-pyrazole structure, 3,4,4-trichloro-1,1-bis[5-(2-naphthyl)pyrazol-1-yl]-2-nitro-1,3-butadiene (**IV**) (Scheme 1).

(*Z*)-3-Chloro-3-(2-naphthyl)propenal (**I**) was converted into the corresponding 2,4-dinitrophenylhydrazone (**V**) in 77% yield by treatment with 2,4-dinitrophenylhydrazine in ethanol in the presence of sodium acetate. However, our attempts to effect heterocyclization of hydrazone **V** by the action of triethylamine or pyridine or by heating at 200°C (15 h) were unsuccessful. In all cases, the initial hydrazone was recovered from the reaction mixtures. Presumably, the presence of two electron-acceptor nitro groups in the benzene ring leads to electron density transfer from the amino group through the conjugated bond system, thus reducing the nucleophilicity of the NH nitrogen atom and preventing intramolecular replacement of the chlorine atom.

The reaction of chloropropenal **I** with *o*-phenylenediamine in methanol saturated with hydrogen chloride involved both the carbonyl group and the chlorine atom, and the product was 2-(2-naphthyl)-1*H*-1,5-benzodiazepine hydrochloride (**VI**, yield 31%).

Scheme 1.



2,4-DNPH is 2,4-dinitrophenylhydrazine.

The structure of products **II** and **IV**–**VI** was determined on the basis of their IR, ^{1}H NMR, and mass spectra and elemental analyses. In the IR spectra of **II** and **IV**–**VI**, stretching vibrations of the C=N bonds give rise to strong absorption bands in the region 1500–1570 cm^{-1}, and broadened bands at 3370, 3285, and 3270 cm^{-1} in the spectra of **II**, **V**, and **VI**, respectively, correspond to N–H stretching vibrations (no NH band was observed for compound **IV**). A broad absorption band with several maxima in the region 2820–2920 cm^{-1} was assigned to the NH$^+$ group of benzodiazepine hydrochloride **VI** [6]. The ^{1}H NMR spectra of compounds **II** and **IV**–**VI** contained multiplet signals from protons in the aromatic fragments and two doublets ($^3J \approx 6$ Hz) due to olefinic protons (=CH) in the heterocyclic (**II**, **IV**, **VI**) or aliphatic moiety (**V**). The N=CH signal in the spectrum of bis-pyrazole **IV** appears at δ 8.90 ppm against δ 7.95 ppm in the

spectrum of initial pyrazole **II** due to the presence of electron-acceptor trichloronitrobutadiene fragment.

In the electron impact mass spectra of **II**, **IV**, and **V**, we observed peaks from the molecular ions and fragment ions formed by elimination of naphthyl fragments, chlorine atoms (**IV**), and nitro groups (**IV**, **V**). The intensity ratio in the $^{35}Cl/^{37}Cl$ isotope cluster in the mass spectrum of bis-pyrazolyl derivative **IV** was equal to 100:98:32, indicating the presence of three chlorine atoms in the molecular ion [7, 8]. Benzodiazepine hydrochloride **VI** showed no molecular ion peak in the mass spectrum, but that from the $[M - HCl]^+$ ion with *m*/*z* 270 was present.

Chloropropenal **I** turned out to be a convenient starting material for the synthesis of isoxazole and pyrimidine derivatives which were obtained by reactions with hydroxylamine and formamide, respectively. Depending on the conditions, the reaction of **I** with hydroxylamine afforded the corresponding oxime (**VII**) or 5-(2-naphthyl)isoxazole (**VIII**). Oxime **VII** was formed in 80% yield in aqueous ethanol in the presence of sodium acetate, whereas in anhydrous methanol in the absence of sodium acetate the product was isoxazole **VIII** (yield 66%). In the latter case, oxime **VII** was isolated as by-product (yield 12%), and a small amount (~5–6%) of 3-chloro-3-(2-naphthyl)-acrylonitrile was identified in the reaction mixture by gas chromatography–mass spectrometry. Litvinov *et al*. previously studied the reaction of 3-(1-adamantyl)-3-chloropropenal with hydroxylamine and reported [9] on the formation of 3-(1-adamantyl)-3-chloroacrylonitrile as by-product. Presumably, oxime **VII** is formed as *syn* isomer; on heating in methanol or in the presence of pyridine, it undergoes heterocyclization to isoxazole structure **VIII**.

β-Chlorovinyl aldehydes are known to react with formamide, yielding pyrimidine derivatives [10]. The reaction of chloropropenal **I** with excess formamide at 190–200°C resulted in formation of 45% of 4-(2-naphthyl)pyrimidine (**IX**). Presumably, the process begins with nucleophilic replacement of the chlorine atom in **I** to give enamino aldehyde **IXa** which then reacts with the second formamide molecule. Here, the formation of pyrimidine ring is analogous to that occurring in reactions of formamide with β-diketones in which the second carbonyl group is equivalent to the =CCl group in **I** [11]. Naphthylpyrimidine **IX** was previously synthesized from 2-acetylnaphthalene [12]; however, its structure was confirmed in [12] only by the UV spectrum and elemental analysis.

Compounds **VII**–**IX** were identified by the IR, ^1H NMR, and mass spectra. In the IR spectra of **VII**–**IX**, C=N stretching vibrations were characterized by absorption bands at 1580–1612 cm^{-1}, and vibrations of the O–H bond in oxime **VII** gave rise to a broad absorption band with its maximum at 3233 cm^{-1}. The ^1H NMR spectrum of **VII** contained a multiplet signal from the aromatic protons and two doublets at δ 8.40 and 6.95 ppm, which were assigned to the olefinic protons in the side chain. In the ^1H NMR spectrum of isoxazole **VIII**, the 4-H signal appeared as a doublet at δ 6.68 ppm (4-H, ^3J = 2.5 Hz), and pyrimidine **IX** displayed a singlet at δ 9.30 ppm (2-H), a doublet at δ 8.92 ppm (6-H, ^3J = 5.6 Hz), and a doublet of doublets at δ 7.51 ppm (5-H, ^3J = 5.6 Hz). The protons in position *1* of the naphthalene ring and in position *5* of the pyrimidine ring in molecule **IX** are coupled through a long-range coupling constant ^5J of 1.5 Hz. In the mass spectra of **VII**–**IX** we observed the corresponding molecular ion peaks.

EXPERIMENTAL

The IR spectra were recorded on a Protege-460 Fourier spectrometer from samples prepared as KBr pellets. The ^1H NMR spectra were recorded from solutions in DMSO-d_6 (**II**, **V**, **IX**) or $CDCl_3$ (**IV**, **VI**–**VIII**) on a Tesla BS-567A instrument (100 MHz) using TMS as internal reference. The mass spectra (electron impact, 70 eV) were obtained using a Hewlett–Packard HP 5972 mass-selective detector which was coupled with an HP 5890 gas chromatograph (HP-5MS capillary column, 30 m×0.25 mm; stationary phase 5% of phenylmethylsilicone; injector temperature 250°C).

5-(2-Naphthyl)pyrazole (II). A mixture of 1.5 g (7 mmol) of chloropropenal **I** and 0.4 g (8 mmol) of hydrazine hydrate in 20 ml of ethanol was heated for 4 h under reflux and was left overnight. It was then poured into 100 ml of distilled water, and the precipitate was filtered off, washed with water and ethanol, and dried under reduced pressure. Yield 1 g (74%), mp 146–148°C. IR spectrum, ν, cm^{-1}: 1504, 1583, 1614 (C=C); 1556 (C=N); 3056 (C–H); 3370 (NH). ^1H NMR spectrum, δ, ppm: 5.7 br.s (1H, NH), 7.0 d (1H, 4-H, pyrazole, ^3J = 6 Hz), 7.40–7.80 m (6H, naphthalene), 7.95 d (1H, 3-H, pyrazole, ^3J = 6 Hz), 8.14 s (1H, 1-H, naphthalene). Found, %: C 80.18; H 4.92; N 14.26. M^+ 194. $C_{13}H_{10}N_2$. Calculated, %: C 80.38; H 5.20; N 14.42. *M* 194.25.

3,4,4-Trichloro-1,1-bis[5-(2-naphthyl)pyrazol-1-yl]-2-nitro-1,3-butadiene (IV). Pentachloro-2-nitro-

1,3-butadiene (**III**), 0.25 g (0.9 mmol), was added dropwise under stirring at room temperature to a solution of 0.7 g (3.6 mmol) of naphthylpyrazole **II** in 30 ml of diethyl ether. The precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure. Yield 0.6 g (82%), mp 198–199°C. IR spectrum, ν, cm^{-1}: 1351, 1603 (NO_2); 1503, 1562 (C=C); 1570 (C=N); 3056 (CH). ^{1}H NMR spectrum, δ, ppm: 7.2–7.4 m (3H, naphthalene), 7.35 d (2H, 4-H, pyrazole, ^3J = 6 Hz), 7.5–7.9 m (9H, naphthalene), 8.31 s (2H, 1-H, naphthalene), 8.90 d (2H, 3-H, pyrazole, ^3J = 6 Hz). Found, %: C 61.32; H 3.19; Cl 18.59; N 11.52. M^+ 585. $C_{30}H_{18}Cl_3N_5O_2$. Calculated, %: C 61.50; H 2.93; Cl 18.16; N 11.96. *M* 586.85.

3-Chloro-3-(2-naphthyl)propenal 2,4-dinitrophenylhydrazone (V). A mixture of 0.99 g (5 mmol) of 2,4-dinitrophenylhydrazine, 1.12 g (5 mmol) of chloropropenal **I**, 0.41 g (5 mmol) of sodium acetate, 30 ml of ethanol, and 5 ml of water was heated for 15 min at the boiling point. The precipitate was filtered off, washed with water and diethyl ether, dried under reduced pressure, and recrystallized from ethanol. Yield 1.7 g (77%), mp 298–300°C. IR spectrum, ν, cm^{-1}: 1317, 1336, 1601, 1615 (NO_2); 1500, 1513, 1533, 1559 (C=N, C=C); 3055, 3105 (CH); 3285 (NH). ^{1}H NMR spectrum, δ, ppm: 7.38 d (1H, CCl=CH, ^3J = 6.1 Hz), 7.5–7.7 m (2H, H_{arom}), 7.9–8.1 m (5H, H_{arom}), 8.35–8.48 m (2H, H_{arom}), 8.85 s (1H, 1-H, naphthalene), 8.93 d (1H, CH=N, ^3J = 6.1 Hz), 11.85 br.s (1H, NH). Found, %: C 57.87; H 3.60; Cl 9.00; N 13.97. M^+ 396. $C_{19}H_{13}ClN_4O_4$. Calculated, %: C 57.51; H 3.30; Cl 8.94; N 14.12. *M* 396.77.

2-(2-Naphthyl)-1*H*-1,5-benzodiazepine hydrochloride (VI). A solution of 1 g (4.6 mmol) of aldehyde **I** in 15 ml of methanol was cooled to 0°C, and a cold suspension of *o*-phenylenediamine hydrochloride in methanol saturated with hydrogen chloride was added in portions. The mixture was stirred for 30 min at 0°C and for 30 min at 20°C. The green precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure. Yield 0.4 g (31%), mp 176–178°C. IR spectrum, ν, cm^{-1}: 1515, 1573, 1589, 1601 (C=C); 1626 (C=N); 2823, 2871, 2918 (NH^+); 2995, 3040, 3052 (CH); 3270 (NH). ^{1}H NMR spectrum, δ, ppm: 6.7 d (1H, 3-H, diazepine, ^3J = 6 Hz), 6.90–7.75 m (10H, H_{arom}), 7.85 d (1H, 4-H, diazepine, ^3J = 6 Hz), 8.18 s (1H, 1-H, naphthalene), 10.0 br.s (1H, NH), 10.7 br.s (1H, NH^+). Found, %: C 74.34; H 5.28; Cl 11.13; N 9.25. $[M - HCl]^+$ 270. $C_{19}H_{15}ClN_2$. Calculated, %: C 74.38; H 4.93; Cl 11.56; N 9.13. *M* 306.78.

3-Chloro-3-(2-naphthyl)propenal oxime (VII). A solution of 7 g (101 mmol) of hydroxylamine hydrochloride in 10 ml of water was added to a solution of 3.25 g (15 mmol) of chloropropenal **I** in 15 ml of ethanol, and a solution of 6 g (73 mmol) of sodium acetate in 30 ml of water was then added under stirring at room temperature. The mixture was diluted with 30 ml of ethanol to obtain a homogeneous solution, stirred for 10 h at 55–60°C, and diluted with water, and the precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 2.78 g (80%), mp 140–141°C (from methanol). IR spectrum, ν, cm^{-1}: 1504, 1610 (C=C); 1600 (C=N); 3024, 3050 (CH); 3233 (OH). ^{1}H NMR spectrum, δ, ppm: 6.95 d (1H, ClC=CH, ^3J = 6.1 Hz), 7.35–7.90 m (6H, naphthalene), 8.20 s (1H, 1-H, naphthalene), 8.40 d (1H, CH=N, ^3J = 6.1 Hz). Found, %: C 67.25; H 4.54; Cl 15.10; N 6.28. M^+ 231. $C_{13}H_{10}ClNO$. Calculated, %: C 67.40; H 4.35; Cl 15.30; N 6.05. *M* 231.67.

5-(2-Naphthyl)isoxazole (VIII). A solution of 1.9 g (9 mmol) of chloropropenal **I** in 25 ml of methanol was added dropwise over a period of 30 min to a solution of 0.7 g (10 mmol) of hydroxylamine hydrochloride in 15 ml of methanol, heated to 60–65°C. The mixture was heated for 1 h at the boiling point, cooled, and poured into 100 ml of distilled water. The precipitate was filtered off, washed with water and hexane, and dried under reduced pressure. Yield 1.15 g (66%), mp 93–95°C. IR spectrum, ν, cm^{-1}: 1507, 1561, 1582 (C=C); 1612 (C=N); 3001, 3028, 3053 (CH). ^{1}H NMR spectrum, δ, ppm: 6.68 d (1H, 4-H, isoxazole, ^3J = 2.5 Hz), 7.5–8.1 m (6H, naphthalene), 8.3–8.4 m (2H, 3-H, isoxazole, and 1-H, naphthalene). Found, %: C 80.04; H 4.57; N 6.82. M^+ 195. $C_{13}H_9NO$. Calculated, %: C 79.98; H 4.65; N 7.18. *M* 396.77.

4-(2-Naphthyl)pyrimidine (IX). Finely powdered chloropropenal **I**, 2.24 g (10 mmol), was added over a period of 20 min to 15 ml (378 mmol) of formamide heated to 190–200°C. The mixture was heated for 1.5 h, cooled, and poured into 100 ml of distilled water. The precipitate was filtered off, washed with water and diethyl ether, and dried under reduced pressure. Yield 0.96 g (45%), mp 130–131°C; published data [12]: mp 129–130°C. IR spectrum, ν, cm^{-1}: 1505, 1540 (C=C); 1580 (C=N); 3025, 3050 (CH). ^{1}H NMR spectrum, δ, ppm: 7.51 d.d (1H, 5-H, pyrimidine, ^3J = 5.6, ^5J = 1.5 Hz), 7.6–7.7 m (2H, naphthalene), 7.9–

8.4 m (4H, naphthalene), 8.85 d (1-H, naphthalene, ^5J = 1.5 Hz), 8.92 d (1H, 6-H, pyrimidine, ^3J = 5.6 Hz), 9.30 s (1H, 2-H, pyrimidine). Found, %: C 81.08; H 4.47; N 13.41. M^+ 206. $C_{14}H_{10}N_2$. Calculated, %: C 81.52; H 4.90; N 13.58. *M* 206.26.

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