1,3-Dipolar cycloadditions of heterocycles X. Reactions of *C*-benzoyl-*N*-phenylnitrone with dihydrothiophene, *N*-methylpyrrole, thiophene, and benzothiophene

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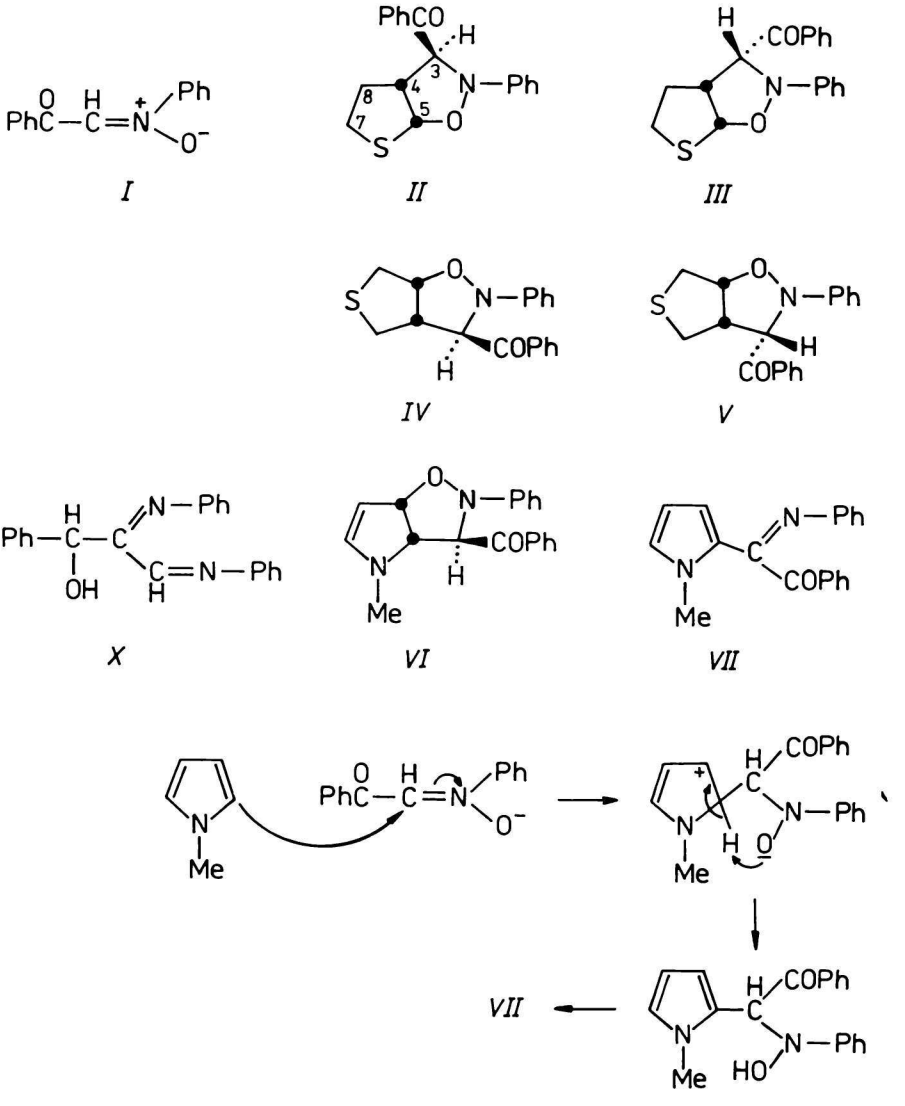
C-Benzoyl-*N*-phenylnitrone reacts with dihydrothiophene derivatives (2,3-dihydro- and 2,5-dihydrothiophene) *via* 1,3-dipolar cycloaddition to give diastereoisomeric pair of *exo*- and *endo*-cycloadducts. In case of *N*-methylpyrrole a substitution product is formed. Thiophene and benzothiophene did not react with the above-mentioned nitrone, decomposition products of nitrone were formed only.

C-бензоил-*N*-фенилнитрон взаимодействует с производными дигидротиофена (2,3-дигидро- и 2,5-дигидротиофен) путем 1,3-диполярного циклоприсоединения с образованием диастереоизомерной пары *экзо*- и *эндо*-циклоаддуктов. В случае *N*-метилпиррола образуется продукт замещения. Тиофен и бензотиофен не реагируют с упомянутым нитроном, образуются лишь продукты разложения нитрона.

1,3-Dipolar cycloadditions of *C*-benzoyl-*N*-phenylnitrone (*I*) with alkenes afford regioisomeric isoxazolidines due to two possible orientations of the reactants [1]. Each orientation can give two diastereoisomeric isoxazolidines on the basis of two possible *endo*- and *exo*-arrangements of the transition states [2, 3]. In previous reports we dealt with 1,3-dipolar cycloadditions of nitrone *I* with furan [4—7], furo-fused [8], and indole derivatives [9]; *I* reacted with high degree of regioselectivity and stereospecificity to give the *endo*-cycloadducts only. On the other hand, 2,3- and 2,5-dihydrofuran [10] as well as oxanorbornadiene and oxanorbornene derivatives [11] reacted under the formation of *endo*- and *exo*--cycloadducts as secondary orbital interactions were not possible.

The present paper deals with 1,3-dipolar cycloadditions of nitrone *I* to 2,3- and 2,5-dihydrothiophene (secondary orbital interactions not possible), *N*-methylpyrrole, thiophene, and benzothiophene (interactions possible). Physical and analytical data of the newly prepared derivatives (Scheme 1) are presented in Experimental. Elemental analysis, mass, u.v., and i.r. spectra indicated formation



Scheme 1

of 1,3-cycloaddition products with dihydrothiophene derivatives and 1,3-addition product with *N*-methylpyrrole. The stereochemical structure was determined from ^{1}H-n.m.r. spectra; chemical shifts and coupling constants are presented in Experimental. The following results were obtained.

2,3-Dihydrothiophene

Both isolated compounds *II* and *III* showed the presence of molecular peak $M^{+\cdot}$ of $\{m/z\} = 311$ pointing to 1:1 cycloadduct, the u.v. spectra were characteristic of isoxazolidines ($\lambda_{max} = 245$ nm). ^{1}H-n.m.r. spectrum of the compound *II* showed a distinct doublet at $\delta = 6.25$ ppm and a therewith coupled multiplet at 3.87 ppm indicating a head-to-head regioisomer analogously as in the case of 2,3-dihydrofuran [10]. The down-field shift $\delta = 6.25$ ppm was due to shielding by two heteroatoms O and S. The coupling constant $J_{4,5} = 6.6$ Hz confirmed *cis* stereospecificity of 1,3-dipolar cycloaddition of nitrone *I* to 2,3-dihydrothiophene. The ^{1}H-n.m.r. spectrum revealed still another doublet at 4.67 ppm with the coupling constant $J_{3,4} = 5.2$ Hz assigned to isoxazolidine 3-H proton, which was proved by decoupling experiment at 309.6 Hz (resonance of the 4-H proton). Doublets of the bridge protons in the diastereoisomeric adduct *III* absorbed at 6.02 ppm and 4.25 ppm. The isoxazolidine 3-H proton appeared in the spectrum as a doublet at 5.04 ppm with high value of the coupling constant $J_{3,4} = 8.4$ Hz. Therefore, we assign this compound, analogously as in the method described in [10] (the Karplus equation, determination of angles from the Dreiding models), the *exo*-structure and the adduct *II* the *endo*-structure. The assignment of the *endo*-adduct follows also from higher value of chemical shift for the bridge 5-H proton due to deshielding by benzoyl group in pseudoaxial position (γ-effect) and lower value of the coupling constant $J_{3,4}$. The ratio of the *endo*- and *exo*-cycloadducts (α) found from integrated intensities in the ^{1}H-n.m.r. spectrum was 76:24 in favour of the *endo*-adduct; in the case of 2,3-dihydrofuran it was 52:48.

2,5-Dihydrothiophene

Since with symmetrical 2,5-dihydrothiophene no regioisomerism is possible, the problem of stereochemistry of the formed adducts was simplified to that of configuration of the isoxazolidine proton. The cycloadduct *V* with chemical shift at $\delta = 5.05$ ppm for the bridge 5-H proton and isoxazolidine 3-H proton at $\delta =$ 5.46 ppm was assigned the *exo*-structure on the basis of its coupling constant $J_{3,4} = 8.5$ Hz. The chemical shift at $\delta = 5.05$ ppm for the bridge 5-H proton, being lower than that in the case of the adducts to 2,3-dihydrothiophene because the

proton here is deshielded with one heteroatom (oxygen) only, confirmed the adduct to 2,5-dihydrothiophene. We failed to separate the diastereoisomeric cycloadduct *IV* from the adduct *V* even by thin layer chromatography. However, the distinct coupling constant $J_{3,4} = 4.3$ Hz in the ^{1}H-n.m.r. spectrum proved its *endo*-structure. The value of α was 34 : 66 in favour of the *exo*-derivative, with 2,5-dihydrofuran it was 44 : 56. With 2,3-dihydrofuran and 2,3-dihydrothiophene more *endo*-derivatives, with 2,5-dihydrofuran and 2,5-dihydrothiophene more *exo*-derivatives were formed.

When studying the reactivity of furan and its derivatives in 1,3-dipolar cycloaddition reactions with nitrones [4—7] we found that nitrone *I* had behaved as an electrophile, *i.e.* the reaction was governed by dominating interaction LUMO (nitrone)—HOMO (furan). On the basis of the known value of the ionization potential of pyrrole 793 kJ mol^{-1}, *i.e.* 8.22 eV mol^{-1} [12] we came to the conclusion that it must be even more reactive than furan (*IP* = 850 kJ mol^{-1}, *i.e.* 8.81 eV mol^{-1}). As in some reactions of pyrrole the N—H bond is attacked we used *N*-methylpyrrole where the methyl group, besides its protecting effect, should reduce the *IP* value and thus increase the reactivity with nitrone *I*.

N-Methylpyrrole

The reactivity of *N*-methylpyrrole in 1,3-dipolar cycloadditions has been described by *Ruccia* and coworkers [13] who used *C*-acetyl-*N*-phenylnitrilimine as 1,3-dipole. In these reactions monocycloadducts or 1,3-addition products were not isolated, two bisadducts were formed only.

We have not isolated from the reaction mixture any cycloaddition products of the *VI* type. The reaction of nitrone *I* with *N*-methylpyrrole proceeding at room temperature for a long time (Experimental), afforded the substitution product (product of 1,3-addition) *VII* (10 %) only. Its structure was assigned on the basis of spectral data and elemental analysis. The ^{1}H-n.m.r. spectrum revealed three doublet-doublets at δ_r/ppm = 6.80, 6.35, and 6.08 with the coupling constants $J_{3,4} = 4.0$ Hz, $J_{3,5} = 1.8$ Hz, $J_{4,5} = 2.8$ Hz characteristic of the monosubstituted pyrrole ring. Also the value of the chemical shift 4.09 ppm belonging to *N*-methyl group proved the pyrrole system (ring current effect). Thus, nitrone *I* must have reacted through its electrophilic carbon (Scheme 1). As the i.r. spectrum did not contain characteristic vibrations of OH group and the mass spectrum showed the presence of the molecular peak $M^{+\bullet}$ $\{m/z\} = 288$, the 1,3-adduct must have been stabilized immediately on elimination of water. In the reactions of nitrone *I* and heterocyclic derivatives with high electron density on carbon neighbouring with the heteroatom, namely 2-methyl- and 2-ethylfuran [5] and *N*-substituted indole derivatives [9], we obtained a substitution product along with 1,3-dipolar cycloaddition. From the reaction mixture also azoxybenzene (12 %) and diketoamide *XI*

(13 %) were isolated. Their formation has been explained in [4] dealing with the reaction of nitrone *I* with furan. The main product isolated was the compound *X* which was formed by hydrogenation of the starting nitrone *I* as we found in [9], where in cycloaddition of indole the formed adduct was dehydrogenated by treatment with nitrone. Probably a similar process took place with *N*-methylpyrrole cycloadducts *VI* as evidenced by formation of the compound *X*. However, in this case the dehydrogenation products were not stable and we failed to identify them. In the reaction with excess *N*-methylpyrrole we could not isolate the appropriate cycloadduct. The reaction accomplished with excess of nitrone (Experimental) resulted in 1,3-addition product *VII* (28 %), azoxybenzene (10 %), hydrogenation product *X* (10 %), diketoamide *XI* (6 %), and benzanilide (8 %).

Cycloadditions of thiophene [14, 15] and benzothiophene [16] with nitriloxides have been described to give negligible yields (<10 %). Their reactions with nitrone *I* gave no 1,3-dipolar cycloaddition products on staying at room temperature for a long time or at 60 °C and 100 °C, respectively. Products of side reactions with structures analogous to those found in the reaction with *N*-methylpyrrole were obtained only.

Experimental

^{1}H-n.m.r. spectra of the synthesized derivatives were measured with a Tesla BS 487 C (80 Hz) apparatus in deuteriochloroform (δ,/ppm) using tetramethylsilane as internal standard. Mass spectra were measured on an MS 902 S spectrometer with direct inlet system at ionization energy 70 eV and 100 μA; the temperature of the ionic source depended on the derivative to be measured. The u.v. spectra were taken with a Specord UV VIS spectrometer in methanol solution. The i.r. spectra were measured with a UR-20 spectrophotometer (Zeiss, Jena) in saturated chloroform solution (NaCl cell 0.6 mm) or by KBr technique. The melting points are not corrected. The reaction course and the purity of compounds were controlled by t.l.c. on silufol plates (detection by UV_{254} light) using cyclohexane—ethyl acetate (volume ratio 4:1) as eluent. Column chromatography of the reaction mixtures evaporated *in vacuo* was performed on silica gel using cyclohexane—ethyl acetate (volume ratio from 6:1 to 2:1) as eluent. Preparative chromatography was accomplished on 20×20 cm plates of 2 mm thickness coated with 45 g silica gel (L_SL_{254}, Lachema, Brno).

C-Benzoyl-*N*-phenylnitrone (*I*) was prepared after [17], 2,3-dihydro- and 2,5-dihydrothiophene by reduction of thiophene with sodium in liquid ammonia [18] and subsequent distillation; *N*-methylpyrrole was a commercial product.

Cycloaddition of I to 2,3-dihydrothiophene

The reaction mixture of *I* (2 g; 8.85 mmol), 2,3-dihydrothiophene (7.5 g; 87.2 mmol), and anhydrous toluene (20 cm^{-3}) was heated in a glass autoclave at 40 °C for 15 h. After

staying at room temperature overnight a yellow crystalline compound *II* (2.1 g, 76 %) with m.p. = 150—152 °C precipitated.

For $C_{18}H_{17}SNO_2$ ($M_r = 311.40$) w_i(calculated): 69.40 % C, 5.46 % H, 4.50 % N; w_i(found): 69.36 % C, 5.42 % H, 3.99 % N.

UV spectrum (methanol) $\lambda_{max} = 247$ nm ($\log \varepsilon = 4.36$). Mass spectrum $M^{+\cdot}$ $\{m/z\} = 311$. ^{1}H-NMR ($CDCl_3$) δ_r/ppm = 6.87—8.25 (m, 10 H, aromatic protons), 6.25 (d, 1 H, $J_{4,5} = 6.6$ Hz, 5-H), 4.67 (d, 1 H, $J_{3,4} = 5.2$ Hz, 3-H), 3.87 (m, 1 H, 4-H), 2.32—2.85 (m, 4 H, 7-H_2 and 8-H_2). ^{1}H-NMR (C_6D_6) δ_r/ppm = 6.75—8.25 (m, 10 H, aromatic protons), 5.87 (d, 1 H, 5-H), 4.30 (d, 1 H, 3-H), 3.50 (m, 1 H, 4-H), 2.12—2.50 (m, 4 H, 7-H_2 and 8-H_2). From the evaporated supernatant *III* (0.66 g, 23 %) of m.p. = 164—166 °C was obtained by preparative thin layer chromatography.

For $C_{18}H_{17}SNO_2$ ($M_r = 311.40$) w_i(calculated): 69.40 % C, 5.46 % H, 4.50 % N; w_i(found): 69.52 % C, 5.23 % H, 4.78 % N.

UV spectrum (methanol) $\lambda_{max} = 247$ nm ($\log \varepsilon = 4.30$). Mass spectrum $M^{+\cdot}$ $\{m/z\} = 311$. ^{1}H-NMR ($CDCl_3$) δ_r/ppm = 6.70—8.25 (m, 10 H, aromatic protons), 6.02 (d, 1 H, $J_{4,5} = 6.5$ Hz, 5-H), 5.04 (d, 1 H, $J_{3,4} = 8.4$ Hz, 3-H), 4.25 (m, 1 H, 4-H), 2.63—3.25 (m, 4-H, 7-H_2 and 8-H_2).

Cycloaddition of I to 2,5-dihydrothiophene

Column separation of the reaction mixture of *I* (2 g; 8.85 mmol), 2,5-dihydrothiophene (7.5 g; 87.2 mmol), and anhydrous toluene (20 cm³) (reaction conditions the same as with 2,3-dihydrothiophene) afforded a yellow crystalline compound *V* (1 g, 36.2 %).

For $C_{18}H_{17}SNO_2$ ($M_r = 311.40$) w_i(calculated): 69.40 % C, 5.46 % H, 4.50 % N; w_i(found): 69.76 % C, 5.42 % H, 4.23 % N.

UV spectrum (methanol) $\lambda_{max} = 247$ nm ($\log \varepsilon = 4.36$). Mass spectrum $M^{+\cdot}$ $\{m/z\} = 311$. ^{1}H-NMR ($CDCl_3$) δ_r/ppm = 6.87—8.25 (m, 10 H, aromatic protons), 5.46 (d, 1 H, $J_{3,4} = 8.5$ Hz, 3-H), 5.05 (m, 1 H, $J_{4,5} = 6.0$ Hz, 5-H), 2.50—3.17 (m, 5 H, 4-H, 6-H_2 and 8-H_2).

Cycloaddition of I to N-methylpyrrole

The reaction mixture of *I* (4.5 g; 20 mmol), *N*-methylpyrrole (81 mmol), and anhydrous benzene (40 cm³) was maintained under nitrogen at 60 °C for 10 h. Separation of the reaction mixture by column chromatography gave the substitution product *VII* with m.p. = 96—97 °C, yield 0.8 g (28 %).

For $C_{19}H_{16}N_2O$ ($M_r = 288.34$) w_i(calculated): 79.07 % C, 5.55 % H, 9.71 % N; w_i(found): 78.89 % C, 5.61 % H, 9.72 % N.

UV spectrum (methanol) $\lambda_{max} = 298$ nm ($\log \varepsilon = 4.26$), IR spectrum (chloroform) $\tilde{\nu}$(CO) = 1675 cm^{-1}, mass spectrum $M^{+\cdot}$ $\{m/z\} = 288$. ^{1}H-NMR ($CDCl_3$) δ_r/ppm = 6.76—7.81 (m, 10 H, aromatic protons), 6.80 (d, d, 1 H, $J_{3,5} = 1.8$ Hz, 5-H), 6.35 (d, d, 1 H, $J_{3,5} = 1.8$ Hz, $J_{3,4} = 4.0$ Hz, 3-H), 6.08 (d, d, 1 H, $J_{4,5} = 2.8$ Hz, $J_{3,4} = 4.0$ Hz, 4-H), 4.09 (s, 3 H, N-CH_3).

In addition, azoxybenzene (0.2 g, 10 %), compound *X* (0.3 g, 10 %), benzanilide (0.3 g, 8 %), and diketoamide *XI* (0.25 g, 6 %) were obtained.

From the reaction mixture of nitrone *I* (4 g; 17 mmol), *N*-methylpyrrole (9 g; 110 mmol), and dry benzene (40 cm^3) after staying at room temperature for 30 days and working up similarly as in the previous case, azoxybenzene (0.2 g, 12 %), substitution product *VII* (0.4 g, 10 %), compound *X* (0.8 g, 30 %), and diketoamide *XI* (0.5 g, 13 %) were obtained.

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