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LETTERS TO THE EDITOR

Synthesis and Reactions of Cycloheptane Dienone Derivatives with Hydrazine

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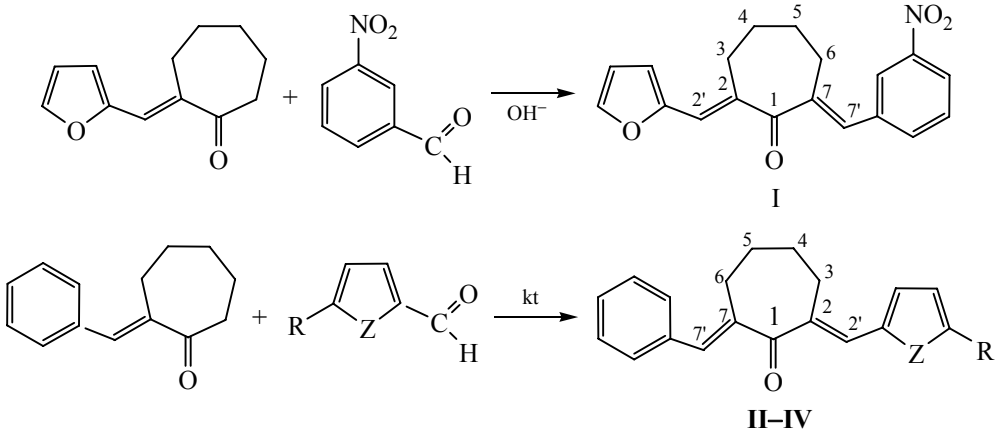
Only few publications describe the synthesis and reactions of symmetrical cross-conjugated 2,7-diarylmethylidene cycloheptanones, their biological activity and derivatives, the cycloheptapyrazolines [1–5]. Asymmetrically built cycloheptane dienone derivatives have not been reported at all. Introduction into their structure of heterocyclic substituents creates unequal electrophilic reaction centers and expands the aspects of their possible practical applications.

This paper presents the data on the synthesis of new dienone derivatives of cycloheptane containing aryl (phenyl, *m*-nitrophenyl) and heterocyclic (furyl, 5-nitrofuryl, thienyl) substituents, and the study of their reactions with hydrazine.

7-Arylmethylidene-2-hetarylmethyledene cycloheptanones **I–IV** were obtained by the condensation of the corresponding monoenone derivatives with aldehydes under alkaline (for dienones **I**, **II**, **IV**) or acidic (for dienone **III**) catalysis.

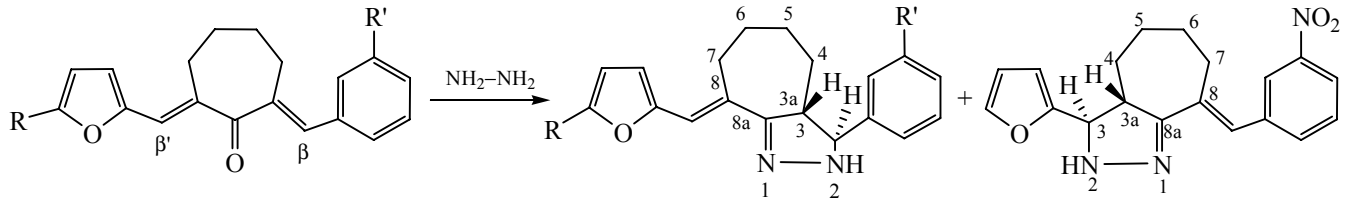


Z = O, R = H (**II**), NO_2 (**III**); Z = S, R = H (**IV**).

Yields of the formed ketones were significantly lower than the yields of their cyclopentane and cyclohexane analogs [6] and did not exceed 30% due to the reduced activity of methylene cycloheptanone owing to the conformational features. The IR spectra of the products contain absorption bands characteristic of conjugated C=O and C=C bonds (1626–1603, 1599–1548 cm^{-1}). The presence of bands of the out-of-plane bending vibrations of C=C–H (950–935 cm^{-1}) and the chemical shifts values of vinyl protons in the ^1H NMR spectrum (7.17–7.37 ppm) indicate that the dienones have *E*,*E*-configuration [6].

In the ^{13}C NMR spectra the signals appear of four sp^3-hybridized carbon atoms of cycloheptane ring [C^4 and C^5 (27.0, 27.9 ppm), C^3 and C^6 (28.1–28.6 ppm)], and 14 sp^2-hybridized carbon atoms of benzene, furan and ethylene fragments (111.9–155.8 ppm), and of carbonyl carbon atom (197.9–199.0 ppm).

Using the dienones **I** and **III** containing the pharmacophore groups (5-nitrofuryl, 3-nitrophenyl) as an example, we studied their reaction with hydrazine hydrate. Refluxing the reactants (dienone:hydrazine hydrate, 1:7) in isopropyl alcohol yields the cyclocondensation products, the cyclohepta[*c*]pyrazolines **V**, **VI**:



I, III **V, VI** **Va**

R = H, R' = NO_2 (**I, V**); R' = H, R = NO_2 (**III, VI**).

When a nitro group is present in the benzene ring, a mixture of regioisomeric cyclohepta[*c*]pyrazolines was formed (**V**:**Va**, 3:1) as a result of azacyclization involving the carbonyl group and the β- and β'-reaction centers of the substrate. In the case of the presence of a nitro group in the furan ring the reaction proceeds regioselectively to form one of the possible regioisomers **VI** due to the strong electron-acceptor effect and the planar arrangement of nitrofuran substituent leading to the activation of the β-carbon atom.

The IR spectra of cycloheptapyrazolines contain the bands of stretching vibrations of the secondary amino group (3339–3340 cm^{-1}), conjugated system C=C–C=N (1558–1616 cm^{-1}), nitro group (1328, 1350, 1501, 1524 cm^{-1}), C–O–C bond (furan) (1030 cm^{-1}). In the ^1H NMR spectra the location of the protons H^3 and N^{3a} (4.37–4.48 and 2.95–3.06 ppm, $J_{3,3a}$ 12 Hz) corresponds to their *trans*-configuration. There are singlets of vinyl (7.31–7.33 ppm) and NH-protons (5.56–6.02 ppm). Assignment of the signals is made on the basis of comparison with the spectra of NH-hexahydroindazoles [7], whose structure was unambiguously established by the X-ray diffraction analysis.

7-(3-Nitrophenylmethylidene)-2-furfurylidenecycloheptanone (I). To a mixture of 3.8 g (20 mmol) of 2-furfurylidenecycloheptanone and 3.0 g (20 mmol) of 3-nitrobenzaldehyde in 5 ml of ethanol was dropwise added 5 ml of 20% alkali. The formed oil was ground with hexane to give fine yellow crystals. Yield 1.3 g (16%), mp 147–149°C (2-propanol). IR spectrum, ν, cm^{-1}: 1662 (C=O), 1560–1624 (C=C), 1022 [C–O–C(Fu)]. ^1H NMR spectrum, δ, ppm, (*J*, Hz): 1.94–2.03 m (4H, H^4, H^5), 2.64–2.88 m (4H, H^3, H^6), 6.49–6.63, 7.17 s (1H, =CH–Ar), 7.33 s (1H, =CH–Fu), 7.52–7.72 (3H, Fu), 8.14–8.30 m (4H, Ar). ^{13}C NMR spectrum, δ_C, ppm: 27.0, 27.4 (C^4, C^5), 28.2, 28.3 (C^3, C^6), 113.0–154.1 ($C^{2,2',7,7'}$, furan, benzene ring), 197.9 (C=O). Found, %: C 70.64; H 5.36; N 4.25. $C_{19}H_{17}NO$. Calculated, %: C 70.59; H 5.26; N 4.33.

7-Benzylidene-2-furfurylidenecycloheptanone (II) was prepared similarly from 1.76 g (8.8 mmol) of 2-benzylidenecycloheptanone and 0.85 g (8.8 mmol) of furfural. Yield 0.6 g (25%), mp 90–92°C (2-propanol). IR spectrum, ν, cm^{-1}: 1626 (C=O), 1548–1603 (C=C), 1016 [C–O–C(Fu)]. ^1H NMR spectrum, δ, ppm, (*J*, Hz): 1.91–1.94 m (4H, H^4, H^5), 2.66–2.86 m (4H, H^3, H^6), 7.31 s (1H, =CH–Fu), 7.24 s (1H, =CH–Ar), 7.32–7.51 m (5H, Ar), 6.47–6.60, 7.32–7.51 (3H, Fu). ^{13}C NMR spectrum, δ_C, ppm: 27.3, 27.8 (C^4, C^5), 28.3, 28.4 (C^3, C^6), 111.9–155.8 ($C^{2,2',7,7''}$, furan, benzene ring), 199.0 (C=O). Found, %: C 81.68; H 7.09. $C_{19}H_{18}O_2$. Calculated, %: C 82.00; H 6.47.

7-Benzylidene-2-(5-nitrofurylmethylidene)cycloheptanone (III). To a mixture of 1.7 g (12 mmol) of 2-benzylidenecycloheptanone and 2.43 g (12 mmol) of 5-nitrofurfural in 5 ml of CH_3COOH was added 1–2 drops of conc. H_2SO_4. Yield 0.47 g (12%), yellow needle crystals, mp 167–168°C (2-propanol). IR spectrum, ν, cm^{-1}: 1667 (C=O), 1558–1626 (C=C), 1022 [C–O–C(Fu)]. ^1H NMR spectrum, δ, ppm, (*J*, Hz): 1.92–2.02 m (4H, H^4, H^5), 2.66–2.93 m (4H, H^3, H^6), 7.31 s (1H, =CH–Ar), 7.33 s [1H, =CH–(5-NO_2)

Fu], 7.32–7.51 m (5H, Ar), 6.68–6.97, 7.32–7.51 [2H, (5-NO_2)Fu]. ^{13}C NMR spectrum, δ_C, ppm: 27.3, 27.9 (C^4, C^5), 28.1, 28.6 (C^3, C^6), 112.0–152.0 ($C^{2,2',7,7'}$, furan, benzene ring), 199.0 (C=O). Found, %: C 71.08; H 5.56; N 4.16. $C_{19}H_{17}NO$. Calculated, %: C 70.59; H 5.26; N 4.33.

7-Benzylidene-2-thienylidenecycloheptanone (IV) was obtained similarly from 2 g (10 mmol) of 2-benzylidenecycloheptanone and 1.12 g (10 mol) of thiophene aldehyde. Yield 0.9 g (30%), mp 132–134°C (2-propanol). IR spectrum, ν, cm^{-1}: 1666 (C=O), 1570–1618 (C=C), 768 [C–S–C(Th)]. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.93–2.12 m (4H, H^4, H^5), 2.63–2.78 m (4H, H^3, H^6), 7.36 s (1H, =CH–Ar), 7.37 s (1H, =CH–Th), 7.06–7.49 (3H, Th), 7.26–7.49 m (5H, Ar). Found, %: C 77.11; H 5.99; S 10.52. $C_{19}H_{18}OS$. Calculated, %: C 77.55; H 6.12; S 10.88.

***trans*-3-(3-Nitrophenyl)-8-(2-furfurylidene)-3,3a-dihydrocyclohepta[*c*]pyrazole (V) and *trans*-3-furyl-8-(3-nitrophenylmethylidene)-3,3a-dihydrocyclohepta[*c*]pyrazole (Va).** A mixture of 0.5 g (1.5 mmol) of 2-(3-nitrophenylmethylidene)-7-(2-furfurylidene)cycloheptanone and 0.5 ml (10 mmol) of hydrazine hydrate in isopropanol was refluxed for 15 min. On cooling, the yellow crystals precipitated. Yield 0.11 g (21%), mp 134–136°C (2-propanol). IR spectrum, ν, cm^{-1}: 3339 (NH), 3161–3092 [CH(Ph)], 1578, 1558 (C=C–C=N), 1524, 1350 (NO_2), 1030 [C–O(Fu)]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18–1.69 m (6H, $H^{4,5,6}$), 1.82–2.25 m (2H, H^7), 2.95–3.03 m (1H, H^{3a}), 4.48 d, 4.42 d (1H, H^3, *J* 12), 5.56 s (1H, NH), 6.96 s (1H, =CH–Fu), 7.24–7.47 m (3H, Fu), 7.47–8.40 m (4H, Ar). Found, %: C 67.19; H 5.83; N 12.78. $C_{19}H_{19}NO$. Calculated, %: C 67.66; H 5.64; N 12.46.

***trans*-3-Phenyl-8-(5-nitro-2-furylmethylidene)-3,3a-dihydrocyclohepta[*c*]pyrazole (VI)** was obtained similarly from 0.16 g (0.5 mmol) of 2-(benzylidene)-7-(5-nitrofurylmethylidene)cycloheptanone and 0.5 ml (10 mmol) of hydrazine hydrate. Yield 0.08 g (48%), mp 113–114°C (2-propanol). IR spectrum, ν, cm^{-1}: 3340 (NH), 3158–3029 [CH(Ph)], 1576, 1616 (C=C–C=N), 1501, 1328 (NO_2), 1030 [C–O–C(Fu)]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39–2.18 m (6H, $H^{4,5,6}$), 2.95–3.06 m (1H, H^{3a}), 3.01–3.06 m (2H, H^7), 4.37 d (1H, H^3, *J* 12), 5.97 s (1H, NH), 6.48–6.49 m [2H, (5-NO_2–Fu], 7.01 s [1H, =CH–(5-NO_2–Fu)], 7.26–7.37 m (5H, Ar). Found, %: C 68.05; H 5.94; N 12.02. $C_{19}H_{19}NO$. Calculated, %: C 67.66; H 5.64; N 12.46.

The IR spectra were recorded on a FSM-1201 Fourier-spectrometer (from KBr pellets). The ^{1}H and ^{13}C NMR spectra were registered on a Varian 400 spectrometer in $CDCl_3$ relative to internal TMS. The reaction progress and purity of the compounds obtained were monitored by TLC method on Silufol UV-254 plates eluting with hexane–2-propanol–chloroform mixture (3:1:1).

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