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2,4-Diazapenta-1,4-dienes in the Synthesis of 2,6-Diaryl-3,5-dinitropiperidines

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Abstract—2,4,6-Triphenyl- and 2,6-diaryl-3,5-dinitropiperidines were synthesized in 70–79% yields by reaction of 1,3,5-triaryl-2,4-diazapenta-1,4-dienes with 2,2-dimethyl- and 2-phenyl-1,3-dinitropropanes.

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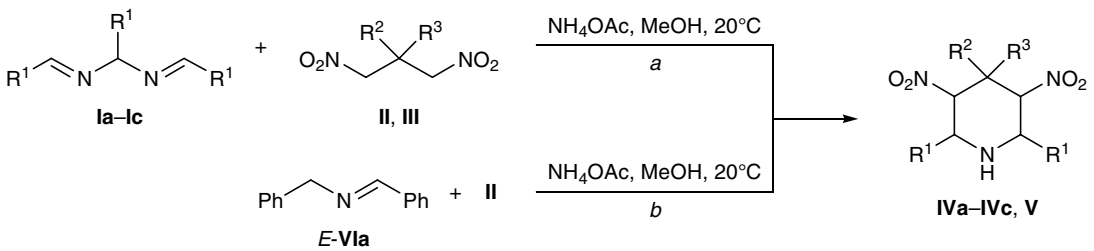
Piperidine derivatives exhibit a broad spectrum of biological activity. Many compounds of this series can be isolated from natural sources or are products of vital activity of microorganisms and fungi [1]. When the concentration of a required compound in a natural object is fairly low, chemical synthesis becomes the main method for their preparation. Therefore, development of new synthetic approaches to piperidine derivatives on the basis of accessible organic compounds is an important problem. For example, 1,3,5-triphenyl-2,4-diazapenta-1,4-diene (**Ia**, hydrobenzamide) which is known since 1837 [2] is presently used in the synthesis of ethane-1,2-diamines [3], derivatives of dihydroimidazole, pyrimidine, and benzoxazine, and some other compounds [4].

Nitrogen-containing heterocycles can be obtained from 2,4-diazapenta-1,4-dienes via reactions with carbonyl compounds and classical CH acids; these reactions involve a series of consecutive transformations leading to different products [5–8]. We have found no published data on reactions of 2,4-diazapentadienes **Ia**–**Ic** with compounds having two activated methylene groups; therefore, we examined reactions of **Ia**–**Ic** with 2-substituted 1,3-dinitropropanes **II** and **III** which were successfully used previously in the synthesis of 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes according to Mannich [9] (Scheme 1).

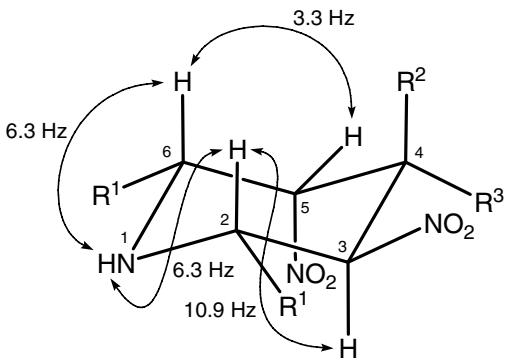
It is known that strong bases promote closure of the bisazomethine system in hydrobenzamides **Ia**–**Ic** to 2,4,5-triaryl-4,5-dihydroimidazoles [10] and that 1,3-dinitro compounds tend to undergo intramolecular cyclization to give dihydroisoxazole derivatives [11]. Therefore, carbanions were generated *in situ* by the action of ammonium acetate on dinitro compounds **II** and **III** in methanol at 20°C according to [5–8]. Unlike the reaction of hydrobenzamide (**Ia**) with malononitrile, which leads to the formation of 2,4,6-triphenylhexahydropyrimidine-5,5-dicarbonitrile and 2,4,6-triphenylpiperidine-3,3,5,5-tetracarbonitrile in an overall yield of 53% [7], compounds **Ia**–**Ic** reacted with

Scheme 1.

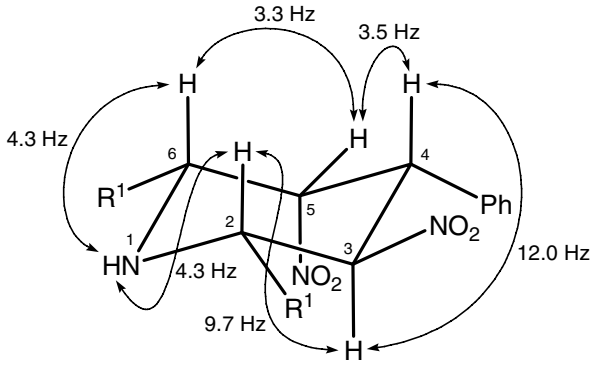


I, **IV**, R^1 = Ph (**a**), $MeOC_6H_4$ (**b**), 2-furyl (**c**); **II**, **IV**, $R^2 = R^3$ = Me; **III**, **V**, R^2 = H, R^3 = Ph.

Scheme 2.



IVa



V

1,3-dinitropropanes **II** and **III** to give 3,5-dinitropiperidines **IVa**–**IVc** and **V** in 70–79% yield (Scheme 1). The formation of cyclic derivatives **IVa**–**IVc** and **V** having only one nitrogen atom in the ring from bisazomethines **Ia**–**Ic** implies elimination of one imine moiety. An analogous pattern was observed in reactions of hydrobenzamide (**Ia**) with mononitro compounds, which resulted in the formation of *N*-benzylidene-2-alkyl-2-nitro-1-phenylpropan-1-amines [7]. It should be noted that the reaction of compound **VIa** (*E* isomer; prepared from benzylamine and benzaldehyde in 82% yield; *Z*/*E* isomer ratio 1:4 [12]) with 2,2-dimethyl-1,3-dinitropropane (**II**) also gave piperidine derivative **IVa** (yield 56%).

The steric structure of dinitropiperidines **IVa**–**IVc** and **V** was determined on the basis of the ^{1}H and ^{13}C NMR data. The proton and carbon signals were assigned using CH correlation technique (CH-CORR). All ring protons in molecule **IVa**, as well as protons in the geminal methyl groups on C^4, are magnetically nonequivalent, indicating that the conformational equilibrium is displaced toward the *chair* conformer. The *trans* arrangement of the nitro groups follows from the spin–spin coupling constants between 5-H and 6-H (^{3}J = 3.3 Hz) and between 2-H and 3-H (^{3}J = 10.9 Hz) (Scheme 2). The latter value is typical of axial orientation of these protons (2-H and 3-H). The direct ^{13}C–^{1}H coupling constants for C^5 and C^3 (142.9 and 155.67 Hz, respectively) also confirm *trans* arrangement of the nitro groups. The ^{1}H NMR spectrum of **IVa** contained two doublets of doublets at δ 4.8 and 5.0 ppm from the 2-H and 6-H protons. These protons are coupled with 3-H and 5-H, respectively (see above), as well as with the NH proton through a constant of 6.3 Hz; the NH proton resonates at δ 2.7 ppm as a triplet. Therefore, the phenyl substituents on C^2 and C^6 are oriented *cis* with respect to each other. The stereochemistry of compounds **IVb** and **IVc** was determined by analogy with **IVa**.

Orientation of the phenyl group on C^4 in molecule **V** was determined on the basis of spin–spin coupling constants between 4-H, on the one hand, and 5-H (^{3}J = 3.5 Hz) and 3-H (^{3}J = 12.0 Hz), on the other. These data correspond to the equatorial orientation of that phenyl group.

Thus 2,6-diaryl-4,4-dimethyl-3,5-dinitropiperidines **IVa**–**IVc** and 3,5-dinitro-2,4,6-triphenylpiperidine (**V**) obtained by reactions of 2,4-diazapenta-1,4-dienes **Ia**–**Ic** with 1,3-dinitropropanes **II** and **III** exist mainly as *chair* conformers with *cis*-2,4,6-*trans*-3,5 configuration of the substituents.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from thin films. The ^{1}H and ^{13}C NMR spectra were measured from solutions in acetone-d_6 on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively; tetramethylsilane was used as internal reference. Thin-layer chromatography was performed on PTSKh-AF-V Sorbfil plates (Krasnodar, Russia). Schiff base **VIa** was synthesized according to the procedure described in [13].

4,4-Dimethyl-3,5-dinitro-2,6-diphenylpiperidine (IVa). *a*. A mixture of 0.300 g (1 mmol) of hydrobenzamide (**Ia**), 0.160 g (1 mmol) of 2,2-dimethyl-1,3-dinitropropane (**II**), and 0.150 g (2 mmol) of ammonium acetate in 5 ml of anhydrous methanol was stirred for 2 days at room temperature. The white precipitate was filtered off, washed with 2 ml of methanol, and dried in air. Yield 0.297 g (78%), mp 181–182°C (from methanol).

b. A mixture of 0.200 g (1 mmol) of Schiff base **VIa**, 0.160 g (1 mmol) of 2,2-dimethyl-1,3-dinitropro-

pane (**II**), and 0.150 g (2 mmol) of ammonium acetate in 5 ml of anhydrous methanol was stirred for 2 days at room temperature. The white precipitate was filtered off, washed with 2 ml of methanol, and dried in air. Yield 0.183 g (56%), mp 181–182°C (from MeOH). IR spectrum, ν, cm^{-1}: 3320 (NH); 1568 (C=C_{arom}); 1548, 1376 (NO_2). ^1H NMR spectrum, δ, ppm: 1.20 s (3H, CH_3), 1.55 s (3H, CH_3), 2.75 t (1H, NH, *J* = 6.3 Hz), 4.80 d.d (1H, 2-H, *J* = 10.9, 6.3 Hz), 5.0 d.d (1H, 6-H, *J* = 6.3, 3.3 Hz), 5.10 d (1H, 5-H, *J* = 3.3 Hz), 5.55 d (1H, 3-H, *J* = 10.9 Hz), 7.20–7.50 m (8H, H_{arom}), 7.60 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.29 (CH_3); 24.81 (CH_3); 37.70 (C^4); 57.38 (C^6); 58.95 (C^2); 91.12 (C^3); 95.80 (C^5); 125.78, 127.70, 128.65, 128.78, 128.89, 128.94, 136.20, 137.83 (C_{arom}). Found, %: C 64.03; H 6.10; N 11.78. $C_{19}H_{21}N_3O_4$. Calculated, %: C 64.21; H 5.96; N 11.82.

2,6-Bis(2-furyl)-4,4-dimethyl-3,5-dinitropiperidine (IVb) was synthesized as described above according to method *a* from compound **Ib**. Yield 79%, mp 116–118°C (from MeOH). IR spectrum, ν, cm^{-1}: 3328 (NH); 1552, 1372 (NO_2); 1508, 1400 (furyl). ^1H NMR spectrum, δ, ppm: 1.30 s (3H, CH_3), 1.50 s (3H, CH_3), 4.90 d.d (1H, 2-H, *J* = 11.2, 10.1 Hz), 5.05 d.d (1H, 6-H, *J* = 10.1, 3.1 Hz), 5.15 d (1H, 5-H, *J* = 3.1 Hz), 5.45 d (1H, 3-H, *J* = 11.2 Hz), 6.30–6.55 m (4H, furyl), 7.50 d (1H, furyl, *J* = 1.7 Hz), 7.65 d (1H, furyl, *J* = 1.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 19.85 (CH_3), 24.12 (CH_3), 37.26 (C^4), 51.85 (C^6), 51.99 (C^2), 69.05 (C^3), 92.45 (C^5), 106.99 and 107.85 (2C, furyl), 109.99 and 110.30 (2C, furyl), 142.54 and 142.86 (2C, furyl), 150.17 and 150.98 (2C, furyl). Found, %: C 53.66; H 5.27; N 12.47. $C_{15}H_{17}N_3O_6$. Calculated, %: C 53.73; H 5.11; N 12.53.

2,6-Bis(4-methoxyphenyl)-4,4-dimethyl-3,5-dinitropiperidine (IVc) was synthesized as described above according to method *a* from compound **Ic**. Yield 76%, mp 212–213°C (from MeOH). IR spectrum, ν, cm^{-1}: 3336 (NH); 2856 (OC–H); 1616 (C=C_{arom}); 1548, 1376 (NO_2). ^1H NMR spectrum, δ, ppm: 1.20 s (3H, CH_3), 1.50 s (3H, CH_3), 2.45 t (1H, NH, *J* = 5.7 Hz), 3.60 s (3H, OCH_3), 3.80 s (3H, OCH_3), 4.65 d.d (1H, 2-H, *J* = 10.9, 5.7 Hz), 4.90 d.d (1H, 6-H, *J* = 5.7, 3.2 Hz), 5.0 d (1H, 5-H, *J* = 3.2 Hz), 5.55 d (1H, 3-H, *J* = 10.9 Hz), 6.85 d (2H, H_{arom}, *J* = 8.8 Hz), 7.0 d (2H, H_{arom}, *J* = 8.8 Hz), 7.30 d (2H, H_{arom}, *J* = 8.8 Hz), 7.50 d (2H, H_{arom}, *J* = 8.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.29 (CH_3); 24.81 (CH_3); 37.70 (C^4); 63.78 (C^6); 67.23 (C^2); 95.41(C^3); 98.73 (C^5); 127.24, 128.69, 128.74, 128.80 (4C, C_{arom}); 132.29, 134.35 (2C, C_{arom}); 160.11, 162.00 (2C, C_{arom}). Found, %: C 60.67; H 6.20; N 10.18. $C_{21}H_{25}N_3O_6$. Calculated, %: C 60.71; H 6.07; N 10.11.

3,5-Dinitro-2,4,6-triphenylpiperidine (V) was synthesized as described above according to method *a* from compound **Ia** and 1,3-dinitro-2-phenylpiperidine (**III**). Yield 70%, mp 94–96°C (from MeOH). IR spectrum, ν, cm^{-1}: 3328 (NH); 1600 (C=C_{arom}); 1552, 1376 (NO_2). ^1H NMR spectrum, δ, ppm: 4.50 d.d (1H, 4-H, *J* = 4.3, 12.0 Hz), 4.55 d.d (1H, 2-H, *J* = 5.3, 9.7 Hz), 5.05 d.d (1H, 6-H, *J* = 3.4, 4.3 Hz), 5.50 d.d (1H, 5-H, *J* = 3.4, 4.3 Hz), 6.10 d.d (1H, 3-H, *J* = 9.7, 12.0 Hz), 7.2–7.7 (15H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 47.92 (C^4); 61.67 (C^6); 65.30 (C^2); 87.75 (C^3); 91.67 (C^5); 126.19–128.91 (15C, C_{arom}); 134.31, 137.60, 138.29 (3C, C_{arom}). Found, %: C 68.56; H 5.31; N 10.38. $C_{23}H_{21}N_3O_4$. Calculated, %: C 68.47; H 5.25; N 10.42.

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