Synthetic Exploitation of the Ring-Opening of 3,4-Dinitrothiophene, VIII[+] Access to 4,5-Dinitro-1,3,5,7-octatetraene Systems

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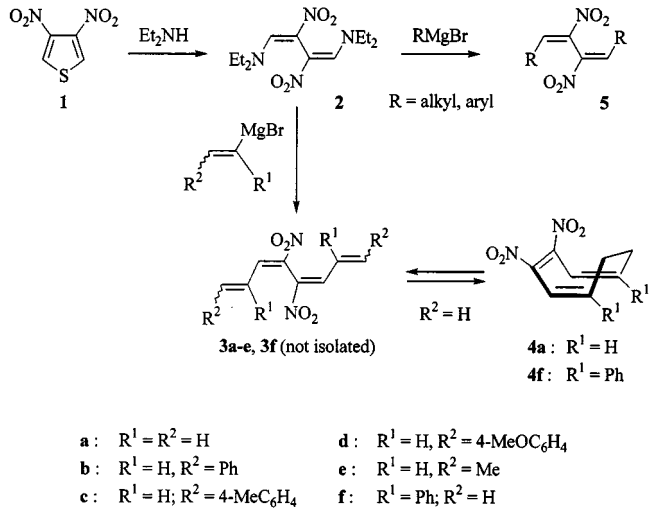
The reactions between 1,4-bis(diethylamino)-2,3-dinitro-1,3-butadiene (**2**), easily obtainable by ring-opening of 3,4-dinitrothiophene with diethylamine, and 2-substituted vinylmagnesium bromides gave good yields of the 4,5-dinitro-1,3,5,7-octatetraene derivatives **3a**–**e**. With 1-phenylmagnesium bromide, conversely, only 3,4-dinitro-1,4-diphenyl-1,3,5-cyclooctatriene (**4f**) was obtained. From the unsubstituted dinitrooctatetraene **3a** both the octatriene cycloisomer **4a** and the valence tautomer of the latter (**6a**) could be isolated and characterized. The results obtained evidence an unfavourable effect of the two nitro groups on the cycloisomerization process of the octatetraene system.

Conjugated polyunsaturated systems are found in a variety of interesting and important organic compounds, including natural products, such as polyene macrolides,[1] pheromones,[2] and carotenoids.[3] Conjugated polyenes, moreover, are considered (also because of their nonlinear optical properties) promising materials for applications in molecular-electronics devices[4] and their importance is consistently evidenced by continuing efforts devoted to the attainment of new synthetic approaches.[2,4,5]



a : $R^1 = R^2 = H$ **d** : $R^1 = H, R^2 = 4\text{-}MeOC_6H_4$
b : $R^1 = H, R^2 = Ph$ **e** : $R^1 = H, R^2 = Me$
c : $R^1 = H; R^2 = 4\text{-}MeC_6H_4$ **f** : $R^1 = Ph; R^2 = H$

Scheme 1

In this framework, we report herein on the synthesis of the hitherto unknown 4,5-dinitro-1,3,5,7-octatetraenes **3** and on their possible cycloisomerization to the corresponding 3,4-dinitro-1,3,5-cyclooctatrienes **4**. The method used (Scheme 1) is an extension of our studies[6] on the use of 3,4-dinitrothiophene (**1**) as template, whereby we have shown how the ring-opening of **1** with diethylamine, followed by treatment of the ensuing 1,4-bis(diethylamino)-2,3-dinitro-1,3-butadiene (**2**) with Grignard reagents,[7] represents an easy access to 1,4-disubstituted 2,3-dinitro-1,3-butadienes **5**: useful building-blocks for the synthesis of variably functionalized aliphatic[7b,8] and heteroaromatic derivatives.[8b,9]

In the light of the potentials, offered by the dinitrobutadienes **5** as intermediates, the research herein was essentially aimed at making easily available compounds **3**, whose utility in synthesis and possible biological activity are in turn surely worth exploring.

Results and Discussion

Reactions of 1,4-Bis(diethylamino)-2,3-dinitro-1,3-butadiene (2) with Vinyl Grignard Reagents

The first reaction investigated was that of the bis(diethylamino)dinitrobutadiene (**2**), easily obtainable by ring-opening from 3,4-dinitrothiophene,[7a,7b,10] with vinylmagnesium bromide in THF at 0°C. Althought TLC analysis of the ongoing reaction showed a smooth conversion of the substrate into a well-defined product, a standard work-up procedure essentially gave a brown gummy material after concentration to dryness of the ethereal extracts. The formation of such tarry material (indicative of some instability of the reaction product, at least in the reaction mixture) could be avoided by a careful work-up essentially through vacuum distillation below 10°C of the ethereal extract to a minimum volume, followed by addition of petroleum ether at 0°C. (*E*,*E*)-4,5-Dinitro-1,3,5,7-octatetraene (**3a**) was thus isolated in 47% yield as pure diastereoisomer. The (*E*,*E*) configuration of **3a** was attributed by ^{1}H NMR on the following grounds: (a) the observation of a single absorption for H(3) and H(6) which rules out an (*E*,*Z*) configuration;

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Table 1. Reactions of vinylic Grignard reagents with 1,4-bis(diethylamino)-2,3-dinitro-1,3-butadiene (**2**)[a]

Entry	Grignard reagent from	Product: yield (%)[b]	Configuration and diastereomeric ratio in **3a**−**e**[c]
1	CH_2=CH−Br[d]	**3a**: 47	*E*,*E*
2	(*E*,*Z*)-PhCH=CH−Br[e]	**3b**: 60	(*E*,*E*,*E*,*E*)/(*Z*,*E*,*E*,*E*) = 48:52
3	(*E*)-4-MeC_6H_4−CH=CH−Br[f]	**3c**: 84	(*E*,*E*,*E*,*E*)/(*Z*,*E*,*E*,*E*) = 70:30
4	(*E*)-4-MeOC_6H_4−CH=CH−Br[f]	**3d**: 86	(*E*,*E*,*E*,*E*)/(*Z*,*E*,*E*,*E*) = 83:17
5	(*Z*)-Me−CH=CH−Br[g]	**3e**: 56	(*E*,*E*,*E*,*E*)/(*Z*,*E*,*E*,*Z*) = 36:64
6	CH_2=C(Ph)Br	**4f**: 69	−

[a] Reactions performed in THF at 0°C with a Grignard reagent/**2** molar ratio of 2.2 for entry 1 and 2.9 for the other entries. − [b] Yields of isolated and purified product are average values of at least two independent experiments. − [c] Determined by ^{1}H NMR of the crude reaction mixture. − [d] Commercial vinylmagnesium bromide (1 M in THF) was employed. − [e] Commercial sample: (*E*)/(*Z*) ≈ 86/14 (^{1}H NMR). − [f] Essentially pure (^{1}H NMR) (*E*) isomer. − [g] Essentially pure (^{1}H NMR) commercial (*Z*) isomer.

(b) the chemical shift value (δ = 7.98) for such a signal, which is consistent with the δ value of ca. 8.2 that can be reckoned for a vinyl hydrogen *cis* to a nitro group in a dinitrooctatetraene system. In fact, starting from the chemical shift values obtained[7a] for the nitrovinyl hydrogen atoms of the (*E*) and (*Z*) portions of 4,5-dinitro-3,5-octadienes (δ = 7.6 and 6.3, respectively) and accounting for the higher deshielding effect of a geminal vinyl group with respect to an ethyl group,[11] δ values of ca. 8.2 and 6.8, respectively, can be expected for nitrovinyl hydrogen atoms in (*E*) or (*Z*) portions of **3a**.

In the light of the results above the reactions of the bis(diethylamino)dinitrobutadiene **2** were likewise performed with a slight excess of Grignard reagents derived either from a 86:14 mixture of (*E*)- and (*Z*)-β-bromostyrene, from (*E*)-4-methyl- and (*E*)-4-methoxy-β-bromostyrene and from (*Z*)-1-bromopropene. The results collected in Table 1 (entries 2−5) show that the reactions performed represent a convenient high-yielding access to 1,8-disubstituted 4,5-dinitro-1,3,5,7-octatetraenes **3b**−**e**, and are encouraging with respect to the general applicability of the method.

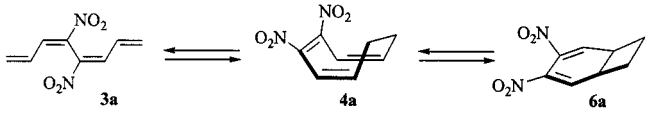
As regards diastereoselectivity of the reactions and configuration of the obtained tetraenes, it is inferred that the configuration around the central C(3)−C(4) and C(5)−C(6) nitrovinyl systems is always (*E*,*E*) as judged by the chemical shift values of the relevant protons *cis* to a nitro group: δ ≈ 8.2 for the aryl-substituted **3b**−**d** and 8.35 for **3e**. Configuration around the C(1)−C(2) and C(7)−C(8) double bonds could be, in turn, easily attributed on the basis of the coupling constants between the relevant hydrogen atoms: average values J_{trans} = 15.3 Hz and J_{cis} = 11.2 Hz. Thus, the diastereomeric ratios reported in Table 1 indicate that in the reactions with **2** the original configuration of the halogenovinyl derivative, precursor of the Grignard reagent, is mainly maintained (86%, on average, for **3b**−**d** and 64% for **3e**). Since we have ^{1}H-NMR evidence that no substantial stereomutation occurs for **3b**−**e** in solution, it is likely that, in agreement with previous results,[12] it essentially occurs along with the preparation of the relevant Grignard reagents, i.e. before the reaction with **2**.

Thus, the method herein appears a convenient access to hitherto unknown 4,5-dinitro-1,3,5,7-octatetraenes whose chemistry and possible biological activity is worth exploring. At the moment, a drawback may be envisaged in the fact that our procedure does not appear to furnish stereochemically well-defined dinitropolyenes. Actually, we were able to separate pure (*E*,*E*,*E*,*E*) diastereomers by chromatography in all cases but for **3e**. This, however, does not mean that an optimized procedure coupled with more sophisticated chromatographic techniques will not allow to reach the desired diastereomerically pure target.

Further interesting aspects of the studied reactions are represented by the results obtained from the reactions of **2** with 1-phenylvinylmagnesium bromide and by some features emerging from a preliminary study of the possible cycloisomerization of representative dinitrooctatetraenes.

Cycloisomerization

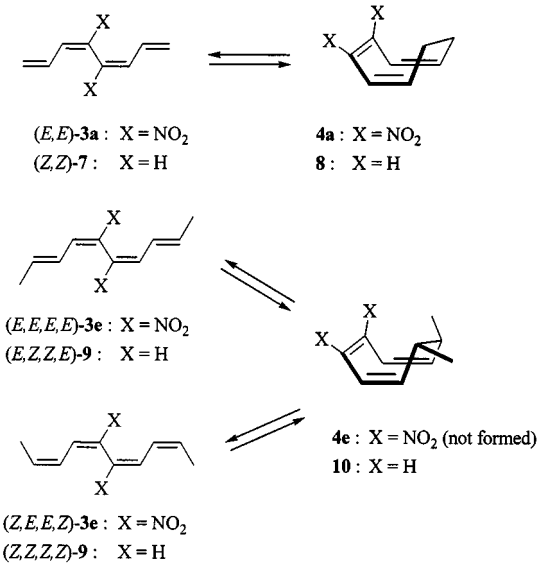
Under conditions identical to those employed with 2-phenylvinylmagnesium bromide (Table 1, entry 2) the treatment of the bis(diethylamino)dinitrobutadiene **2** with 1-phenylvinylmagnesium bromide gave satisfactory yields (Table 1, entry 6) of 3,4-dinitro-1,6-diphenyl-1,3,5-cyclooctatriene (**4f**). In spite of various attempts, also involving reactions and workup at lower temperature, we were unable to isolate and detect even traces of the open-chain dinitrooctatetraene **3f**, the envisageable precursor of **4f**. These findings are clearly indicative of a fast cycloisomerization of **3f** to **4f**.



Scheme 2

As regards cycloisomerization, it is worth noting that an ^{1}H-NMR analysis of the unsubstituted dinitrooctatetraene **3a**, in $CDCl_3$ solution, showed its progressive, even if slow at room temperature, transformation into compounds which were later identified as 3,4-dinitro-1,3,5-cyclooctatriene (**4a**) and its valence tautomer 3,4-dinitro[4.2.0]octa-2,4-diene **6a** (Scheme 2). Further investigations showed that from a chloroform solution of **3a**, kept at room temperature for 48 h, it was possible to isolate by PTLC compound **4a** in an essentially pure form, which was characterized by

^{1}H-, ^{13}C-NMR, and microanalytical data. The successful isolation of **4a** essentially free of **3a** is indicative of a slow **4a** to **3a** equilibration. Successive control experiments showed that $CDCl_3$ solutions of either **3a** or **4a** slowly gave (ca. 48 h at room temperature) a mixture having a **3a**/**4a**/**6a** = 10:63:27 composition. A complete shift of the system toward **6a** was, on the other hand, achieved by heating a chloroform solution of **3a** for 72 h at 60°C; compound **6a** could thus be isolated in almost quantitative yield and fully characterized by ^{1}H, ^{13}C NMR, and microanalysis. The possibility of isolating (*E*,*E*)-**3a** thanks to a slow ring closure to **4a** at 25°C is quite surprising if compared with the reported[13] instability, stemming from a low activation energy (17 kcal/mol) for cyclization of the unsubstituted 1,3,5,7-octatetreane (*Z*,*Z*)-**7** (Scheme 3). Thus, on going from the latter, with a life time of a few seconds, to (*E*,*E*)-**3a**, characterized by the same (*cis*,*cis*) configuration of the carbon skeleton, the introduction of nitro groups in the 4 and 5 positions brings about a substantial increase in the stability of the octatetraene system towards cyclization. The stabilizing effect of the nitro groups is further stressed (Scheme 3) by the failure of **3e** [as the isolated (*E*,*E*,*E*,*E*)/(*Z*,*E*,*E*,*Z*) mixture] as well as of **3b**−**d** to undergo cyclization to the corresponding dinitrocyclooctatriene even after prolonged heating in chloroform. It is relevant to note, for a comparison with **3e**, that both (*E*,*Z*,*Z*,*E*)- and (*Z*,*Z*,*Z*,*Z*)-2,4,6,8-decatetraene **9** [i.e. the tetraenes with the same (*trans*,*cis*,*cis*,*trans*) and (all-*cis*) carbon-skeleton configurations of the two **3e** isomers] do cyclize (ΔG^1 = 20.2 and 25.1 kcal/mol, respectively)[14] although more slowly than (*Z*,*Z*)-**7**.



Scheme 3

The results presented clearly testify in favour of a viable access to a class of synthetically useful nitropolyene intermediates which also undergo structure dependent cycloisomerizations to likewise interesting unsaturated cyclic nitro derivatives.

Ongoing developments encompass: (i) a detailed kinetic analysis in particular of the **3a** → **4a** → **6a** isomerization as well as (ii) an ab initio computational study (at the HF and DFT levels) aimed at clarifying not only the role of the nitro groups in stabilyzing the "linear" dinitrotetraene system herein, as compared to the unsubstituted ones (such as **7** and **9**), but also the influence of other structural parameters (e.g. the presence and position of aromatic rings along the polyene chain) on the relative stability of the open and cyclic systems.

Experimental Section

Melting points were determined with a Büchi 535 apparatus and are uncorrected. − ^{1}H- and ^{13}C-NMR spectra were taken with a Varian Gemini 200 spectrometer in $CDCl_3$ solution (unless otherwise stated); TMS was used as internal standard and chemical shifts are reported as δ values (ppm).

Materials: Petroleum ether and light petroleum refer to the fractions with b.p. 40−60°C and 80−100°C, respectively. Tetrahydrofuran (THF) was purified by standard methods and distilled from potassium benzophenone ketyl before use. 3,4-Dinitrothiophene[15] and (*E*,*E*)-1,4-bis(diethylamino)-2,3-dinitro-1,3-butadiene[7a,7b] (**2**) were synthesized as reported. α-Bromostyrene and β-bromostyrene [(*E*)/(*Z*) ≈ 86:14 (^{1}H NMR)] were commercial samples, distilled before use and dried with 4 Å molecular sieves. (*Z*)-1-Bromo-1-propene was used as received after drying with 4 Å molecular sieves. (*E*)-β-Bromo-4-methylstyrene and (*E*)-β-bromo-4-methoxystyrene were prepared according to a literature method.[16] Vinylmagnesium bromide (nominally 1 M in THF) was a commercial product while the other Grignard reagents were prepared in THF from the corresponding bromo derivatives using standard methods. All the solutions of Grignard reagents were titrated just before use, using a reported procedure.[17] Column (or preparative plate, PTLC) chromatographies were performed on silica gel using petroleum ether and gradients (or appropriate mixtures) with CH_2Cl_2, Et_2O, or AcOEt as eluants, the solvents being distilled before use.

Reactions of 1,4-Bis(diethylamino)-2,3-dinitro-1,3-butadiene (2) with Vinylic Grignard Reagents: In a flame-dried two-neck flask, equipped with an argon inlet, a rubber septum, and a magnetic stirring bar, 1.75 mmol of 1,4-bis(diethylamino)-2,3-dinitro-1,3-butadiene was suspended in 100 mL of THF and cooled to ca. 0°C with an external ice bath; the Grignard reagent in THF (3.85 mmol of vinylmagnesium bromide or 5 mmol of the other reagents) was slowly added by syringe under magnetic stirring. The reaction mixture was kept at the same temperature for 30−45 min (the end of reaction being judged by TLC analysis), then poured into ice/3% HCl (50 mL) and 100 mL of diethyl ether. After separation of the two layers, the aqueous phase was extracted with diethyl ether and the organic phase dried with Na_2SO_4 and a little silica gel to remove traces of tarry material. Concentration of the ether extracts, under vacuum and at ca. 10°C, to a small volume followed by insolubilization with petroleum ether at 0°C gave the products, pure or as diastereomeric mixtures.

Compounds 3a−e and 4f from the Reactions of 2 with Vinylic Grignard Reagents

(*E*,*E*)-4,5-Dinitro-1,3,5,7-octatetraene (3a): M.p. 72.8−73.1°C (petroleum ether). − ^{1}H NMR: δ = 5.92 (2 H, dd, *J* = 8.9 and 2.1 Hz), 6.09 (2 H, dd, *J* = 16.6 and 2.1 Hz), 6.25 (2 H, ddd, *J* = 16.6, 10.5 and 8.9 Hz) and 7.98 (2 H, d, *J* = 10.5 Hz). − ^{13}C NMR:

δ = 129.14, 134.31, 139.65, 140.19.[18] − $C_8H_8N_2O_4$ (196.2): calcd. C 49.0, H 4.1, N 14.3; found C 48.8, H 4.4, N 14.5.

4,5-Dinitro-1,8-diphenyl-1,3,5,7-octatetraenes 3b: The pure (*E*,*E*,*E*,*E*) diastereoisomer could be isolated by PTLC, m.p. 164.0−166.0°C (dec.) (dichloromethane/petroleum ether). − ^{1}H NMR: δ = 6.62 (2 H, dd, *J* = 15.4 and 11.8 Hz), 7.39 (12 H, m) and 8.24 (2 H, dd, *J* = 11.8 and 0.7 Hz). − $C_{20}H_{16}N_2O_4$ (348.4): calcd. C 69.0, H 4.6, N 8.0; found C 69.2, H 4.8, N 7.9. − The ^{1}H-NMR spectrum of (*Z*,*E*,*E*,*E*)-**3b** could be deduced from that of a mixture enriched (PTLC) in that diastereoisomer: δ = 6.15 (1 H, dd, *J* = 12.1 and 11.2 Hz), 6.62 (1 H, dd, *J* = 15.7 and 11.8 Hz), 7.22 (1 H, d, *J* = 11.2 Hz), 7.40 (11 H, m), 8.22 (1 H, d, *J* = 11.8 Hz) and 8.51 (1 H, d, *J* = 12.1 and 1.1 Hz).

1,8-Bis(4-methylphenyl)-4,5-dinitro-1,3,5,7-octatetraenes 3c: A chromatographically pure sample of the (*E*,*E*,*E*,*E*) isomer could be isolated, m. p. ca. 75°C (dec.). − ^{1}H NMR: δ = 2.34 (6 H, s), 6.57 (2 H, dd, *J* = 15.5 and 11.7 Hz), 7.14 (4 H, AA′ of AA′BB′, *J* = 8.1 Hz), 7.32 (6 H in all, 4H BB′ of AA′BB′, *J* = 8.1 Hz and 1 H, d, *J* = 15.5 Hz) and 8.23 (2 H, d, *J* = 11.7 Hz). − The ^{1}H-NMR spectrum of (*Z*,*E*,*E*,*E*)-**3c** was deduced from that of a diastereomeric mixture: δ = 2.37 (3 H, s), 2.44 (3 H, s), 6.10 (1 H, dd, *J* = 12.1 and 11.2 Hz), 6.56 (1 H, dd, *J* = 15.7 and 11.8 Hz), 7.26 (10 H, m), 8.22 (1 H, d, *J* = 11.8 Hz) and 8.52 (1 H, d, *J* = 12.1 Hz). − $C_{22}H_{20}N_2O_4$ (376.4, diastereomeric mixture): calcd. C 70.2, H 5.4, N 7.4; found C 68.9, H 5.2, N 7.4.

1,8-Bis(4-methoxyphenyl)-4,5-dinitro-1,3,5,7-octatetraenes 3d: A chromatographically pure sample of the (*E*,*E*,*E*,*E*) isomer could be isolated, m. p. ca. 100°C (dec.). − ^{1}H NMR: δ = 3.81 (6 H, s), 6.48 (2 H, dd, *J* = 15.3 and 11.7 Hz), 6.86 and 7.41 (4 H each, AA′BB′, *J* = 8.8 Hz), 7.29 (2 H, d, *J* = 15.3 Hz) and 8.22 (2 H, d, *J* = 11.7 Hz). − The ^{1}H-NMR spectrum of (*Z*,*E*,*E*,*E*)-**3d** was deduced from that of a diastereomeric mixture: δ = 3.84 (3 H, s), 3.90 (3 H, s), 6.05 (1 H, dd, *J* = 12.2 and 11.1 Hz), 6.47 (1 H, dd, *J* = 15.2 and 11.8 Hz), 6.88 (2 H, AA′ of AA′BB′, *J* = 8.8 Hz), 7.02 (2 H, AA′ of AA′BB′, *J* = 8.8 Hz), 7.11 (1 H, d, *J* = 11.1 Hz), 7.29 (1 H, d, *J* = 15.2 Hz), 7.41 (4 H, 2 BB′ of AA′BB′ partially overlapped, *J* = 8.8 Hz), 8.21 (1 H, d, *J* = 11.8 Hz) and 8.54 (1 H, d, *J* = 12.2 Hz). − $C_{22}H_{20}N_2O_6$ (408.4, diastereomeric mixture): calcd. C 64.7, H 4.9, N 6.9; found C 64.7, H 4.8, N 7.1.

5,6-Dinitro-2,4,6,8-decatetraenes 3e: Crude, almost diastereomerically pure (*Z*,*E*,*E*,*Z*)-**3e** was obtained by PTLC as a waxy solid. − ^{1}H NMR: δ = 2.06 (6 H, dd, *J* = 7.4 and 1.8 Hz), 5.90 (2 H, ddq, *J* = 11.4, 10.7 and 1.8 Hz), 6.38 (2 H, dqd, *J* = 10.7, 7.4 and 1.0 Hz) and 8.35 (2 H, dd, *J* = 11.4 and 1.0 Hz). − The ^{1}H-NMR spectrum of (*E*,*E*,*E*,*E*)-**3e** was deduced from that of a diastereomeric mixture: δ = 1.96 (6 H, dd, *J* = 7.0 and 1.6 Hz), 5.94 (2 H, ddq, *J* = 14.9, 11.5, and 1.6 Hz), 6.65 (2 H, dqd, *J* = 14.9, 7.0, and 0.8 Hz) and 7.97 (2 H, d, *J* = 11.5 Hz). − $C_{10}H_{12}N_2O_4$ (224.2, diastereomeric mixture): calcd. C 53.6, H 5.4, N 12.5; found C 54.0, H 5.6, N 12.7.

3,4-Dinitro-1,6-diphenyl-1,3,5-cyclooctatriene (4f): M.p. 104.0−105.0°C (dec.) (diethyl ether/methanol). − ^{1}H NMR: δ = 3.08 (4 H, s), 6.54 (2 H, s) and 7.40 (10 H, m). − ^{13}C NMR: δ = 29.60, 115.44, 126.36, 128.89, 129.80, 140.16, 142.97, and 155.40. − $C_{20}H_{16}N_2O_4$ (348.4): calcd. C 69.0, H 4.6, N 8.0; found C 68.4, H 4.8, N 8.1.

Cyclized Compounds from (*E*,*E*)-4,5-Dinitro-1,3,5,7-octatetraene (3a): The dinitro octatetraene **3a** (0.1g, 0.51 mmol), dissolved in $CHCl_3$ (50 mL), was left to stand 48 h at room temperature. Concentration of the solution under vacuum at 10°C followed by a fast chromatography on preparative plates allowed separation, from some starting material, of essentially pure 3,4-dinitro-1,3,5-cyclooctatriene (**4a**) and 3,4-dinitrobicyclo[4.2.0]octa-2,4-diene (**6a**), respectively, in 50 and 22% yield of isolated compounds. Higher yields (> 90%) of **6a** were obtained from a $CHCl_3$ solution of **3a** heated at 60°C for 72 h.

3,4-Dinitro-1,3,5-cyclooctatriene (4a): Yellow oil. − ^{1}H NMR: δ = 2.62 (4 H, m), 6.20 (2 H, d, *J* = 11.7 Hz) and 6.49 (2 H, dm, *J* = 11.7 Hz). − ^{13}C NMR: δ = 26.44, 118.65, 141.95, and 144.72. − $C_8H_8N_2O_4$ (196.2): calcd. C 49.0, H 4.1, N 14.3; found C 48.9, H 4.5, N 14.0.

3,4-Dinitrobicyclo[4.2.0]octa-2,4-diene (6a): M.p. 90.0−91.2°C (light petroleum/toluene). − ^{1}H NMR: δ = 2.56 (4 H, m), 3.47 (2 H, m) and 6.91 (2 H, dd, *J* = 3.3 and 2.1 Hz). − ^{13}C NMR: δ = 31.26, 33.39, 134.89, and 142.54. − $C_8H_8N_2O_4$ (196.2): calcd. C 49.0, H 4.1, N 14.3; found C 49.1, H 4.4, N 13.8.

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