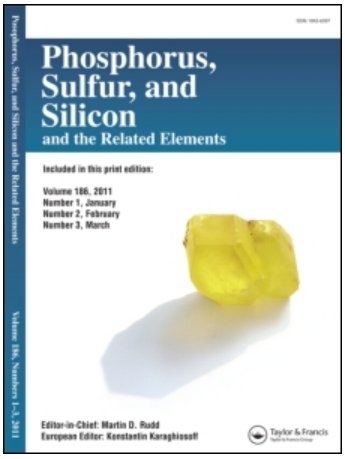

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SOME NEW S-, S,S- AND N,S-SUBSTITUTED 2-NITRODIENES AND BUTADIENYL-SUBSTITUTED PIPERAZINES

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SOME NEW S-, S,S- AND N,S-SUBSTITUTED 2-NITRODIENES AND BUTADIENYL-SUBSTITUTED PIPERAZINES

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*Nitrodiene **1** reacted with **2a,b** and gave the novel compounds **3a,b**, **4a,b**, and **5a**. Monosubstituted diene compound **3a** gave the compounds **9a** with morpholine, **11a** with piperidine, and **13a** with homopiperazine. Compound **3a** gives the thioether compound **15** by the reaction with the dithiol ($HS{-}(CH_2)_2{-}O{-}(CH_2)_2{-}SH$) in ethanol containing sodium hydroxide.*

Keywords: 2-Nitrodiene; dibutadienyl piperazine; dibutadienyl piperidine; homopiperazine; monothiosubstituted dienes; morpholine; thiols

It has been reported before in a U.S. patent that some thio-substituted dienes exhibit high biological activity.[1] The reactions of thiols with hexachlorobutadiene ($Cl_2C{=}CCl{-}CCl{=}CCl_2$), perchlorobutadiene ($Cl_2C{=}CH{-}CCl{=}CCl_2$), and 1H-pentachlorobutadiene ($Cl_2C{=}CCl{-}CCl{=}CH{-}Cl$) have been observed previously.[2–5] Thiosubstituted butadienes, butatrienes, and butenins have been obtained from these reactions,[6–13] and N,N-, N,S-, N,O-, and O,S-substituted 1,3-nitrobutadiene compounds have been published before.[14–17]

It is known that some crown ethers and thio crown ethers give some complex compounds with alkali metals. Moreover some heterocyclic compounds from the reactions of 2-nitrodiene and mono(thio) substituted nitrodienes ($Cl_2C{=}CCl{-}C(NO_2){=}CCl(SR)$) with dithiols were obtained. In these reactions, compounds carrying a diene with a –S–S– group in the ring and some open-chain compounds were also obtained.[18–23]

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Our aim in this study was to synthesize and characterize new S,S- and S,N-substituted nitrodiene compounds from the reactions of some new mono(thio)substituted 2-nitrobutadienes with various thiols, piperazin, and piperidine.

The reaction of 1 mole 2-nitrodiene **1** with 1 mole thiol gives only one reaction product after mixing them for a long time without solvent. However 2-nitrodiene gave two thiosubstituted diene compounds (mono- and di-) with p-methoxy thiophenol. This is probably due to the inductive and resonance effect of the methoxy group on the ring.

2-Nitrodiene **1** reacted with thiols **2a**,**b** and gave **3a**,**b**, and **4b** after mixing them for a long time. 2-Nitrodiene **1** gave **4a**, **5a**, and **4b** in the reaction with **2a**,**b** in EtOH containing sodium hydroxide.

Compounds **3a**,**b** are unknown new mono(thio)substituted diene compounds. Compounds **4a**,**b** are also unknown new bis(thio)substituted diene compounds, and **5a** is a new tris(thio)substituted diene compound. These new compounds are stable, and some of them are yellow in color. The structure of the reaction products were verified by microanalysis and spectroscopic data such as IR, MS, and ^{1}H NMR. We have obtained mono- and disubstituted amine compounds from the reactions of monothiosubstituted dienes with some amines (piperazine, piperidine, etc.) before. The piperazine compounds are important for therapeutical use and also some piperazine compounds were used in gen transfer.[24–26] Compounds **7a–e** were obtained from the reactions of **3a**,**b** with piperazine derivates **6a–e**.

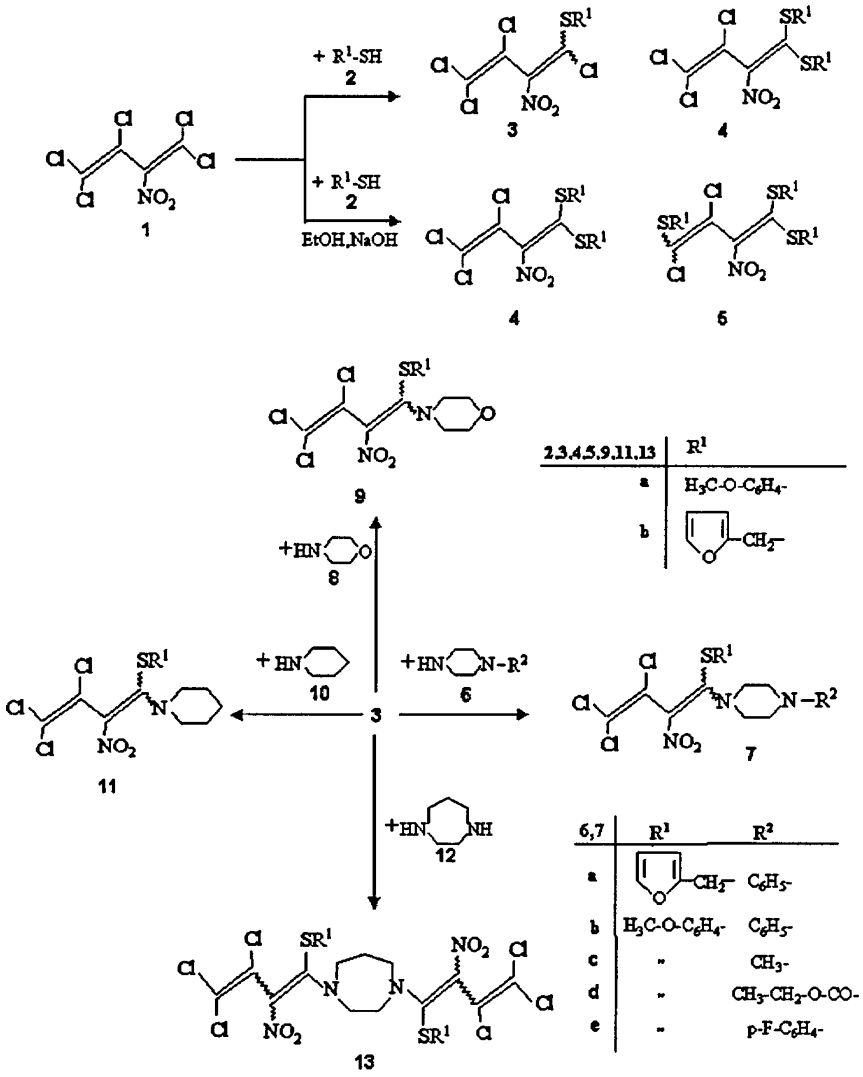
The IR spectrum of **7d** showed a characteristic >C=O band in the 1720 cm^{-1} region.

Compounds **7a–e** are stable monobutadienyl-substituted piperazines. Compound **3a** gave the N,S-substituted diene compound **9a** with morpholine, **11a** with piperidine, and **13a** with homopiperazine (Scheme 1).

Compound **3a** reacted with 2,2′-oxydiethanthiol (HS–$(CH_2)_2$–O–$(CH_2)_2$–SH) **14** and gave the compound **15**. Compound **15** is an unsaturated interesting compound that has a cyclic structure (Scheme 2).

EXPERIMENTAL SECTION

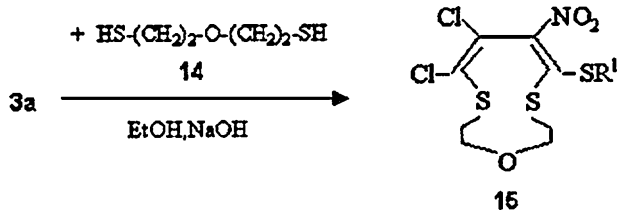
^{1}H NMR: Bruker AC 200 L. IR: Shimadzu Fourier transform infrared (FTIR) 8101. Microanalyses: Carlo-Erba 1110 elemental analyzer. Melting Points: Büchi SMP 20. Products were isolated by column chromatography on SiO_2 (Fluka Kieselgel 60, particle size 63–200 μm). TLC plates silica: 60 F254 (Merck, Darmstadt), detection with ultraviolet light (254 nm).



SCHEME 1

Preparation of S-Substituted Polyhalonitrodienes: General Procedure I

Equimolar amounts of 2-nitro-1,3,4,4-pentachloro-1,3-butadiene **1** and thiols were stirred for 36 h at room temperature until completion of the reaction. Chloroform was added to the reaction mixture. The organic layer was separated and washed with water (4 × 30 ml) and dried



SCHEME 2

with $CaCl_2$ or $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel.

2-Nitro-1,3,4,4-tetrachloro-1-(4-methoxyphenylthio)-1,3-butadiene (3a)

Yellow oil. Yield, 0.585 g (42%). R_f = 0.571 (CCl_4). –IR (film): ν = 2950, 3050 cm^{-1} (C–H), 1650 (C=C), 1250, 1550 (C–NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): δ = 3.7–4.0 ppm (m, 3H, OCH_3), 6.9–7.6 (m, 4H, $H_{arom.}$). $C_{11}H_7SNCl_4O_3$ (375.06) Calcd.: C, 35.23; H, 1.88; N, 3.73. Found: C, 35.46; H, 2.34; N, 4.18. MS m/z 374.9.

2-Nitro-1,3,4,4-tetrachloro-1-(2-furanylmethanethio)-1,3-butadiene (3b)

Yield, 0.995 g (77%). m.p. 64–65°C. R_f = 0.888 (CCl_4). IR (KBr): ν = 2900, 3000, 3100 cm^{-1} (C–H), 1610 (C=C), 1240, 1540 (C–NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): δ = 4.4–4.6 ppm (m, 2H, S–CH_2), 6.3–7.5 (m, 3H, H_{arom}). $C_9H_5SNCl_4O_3$ (349.021). MS m/z 348.9.

2-Nitro-3,4,4-trichloro-1,1-bis(4-methoxyphenylthio)-1,3-butadiene (4a)

Yield, 0.835 g (47%). m.p. 105–106°C. R_f = 0.285 (CCl_4). IR (KBr): ν = 2950, 3000 cm^{-1} (C–H), 1595 (C=C), 1280, 1520 (C–NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): δ = 3.7–4.0 ppm (m, 6H, 2 OCH_3), 6.6–7.2 (m, 8H, H_{arom}). $C_{18}H_{14}S_2NCl_3O_4$ (478.805) Calcd.: C, 45.15; H, 2.94; N, 2.92. Found: C, 45.78; H, 2.85; N, 2.75. MS m/z 478.9.

Preparation of S,S-Substituted Polyhalonitrodienes: General Procedure II

To a mixture of thiols and **1** or monosubstituted dienes in 30 ml of ethanol, 2 g of NaOH (in 10 ml of water) was added at room temperature. The mixture was stirred for 1 h until completion of the reaction. Chloroform was added to the reaction mixture. The organic layer was separated and washed with water (4 × 30 ml) and dried with $CaCl_2$ or

$MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel.

2-Nitro-3,4,4-trichloro-1,1-bis(2-furanylmethanethio)-1,3-butadiene (4b)

Brown oil. Yield, 0.585 g (37%). $R_f = 0.866$ ($CHCl_3$). IR (film): $\nu =$ 2950, 3050 cm^{-1} (C—H), 1590 (C=C), 1280, 1550 (C—NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): $\delta = 3.6–4.5$ ppm (m, 4H, 2S—CH_2), 6.9–706 (m, 6H, $H_{arom.}$). $C_{14}H_{10}S_2NCl_3O_4$ (426.728). MS m/z 425.9.

2-Nitro-1,1,4-tris(4-methoxyphenylthio)-3,4-dichloro-1,3-butadiene (5a)

Yield, 1.548 g (72%). m.p. 147–148°C. $R_f = 0.925$ ($CHCl_3$). IR (KBr): $\nu =$ 2850, 2950, 3020 cm^{-1} (C—H), 1650 (C=C), 1250, 1510 (C—NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): $\delta = 3.6–3.9$ ppm (m, 9H, 3 OCH_3), 6.5–7.5 (m, 12H, $H_{arom.}$) $C_{25}H_{21}S_3NCl_2O_5$ (582.549) Calcd.: C, 51.55; H, 3.63; N, 2.40. Found: C, 51.37; H, 3.40; N. 2.23.

5-(4-Methoxyphenylthio)-6-nitro-7,8-dichloro-4,9-dithia-1-oxacycloun-decane-5,7-diene (15)

Yield, 0.132 g (56%). m.p. 99–100°C. $R_f = 0.667$ ($CHCl_3$). IR (KBr): $\nu =$ 2850, 2950 cm^{-1} (C—H), 1590 (C=C), 1250, 1290, 1530 (C—NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): $\delta = 2.5–3.6$ ppm (m, 8H, $(CH_2)_2$—O—$(CH_2)_2$), 3.7–4.0 (m, 3H, OCH_3), 6.6–7.4 (m, 4H, $H_{arom.}$). $C_{15}H_{15}S_3NCl_2O_4$ (440.39) Calcd.: C, 40.91; H, 3.43; N, 3.18. Found: C, 40.67; H, 3.49; N, 3.12.

Preparation of N,S-Substituted Polyhalonitrodienes: General Procedure III

Equimolar amounts of S-substituted polyhalonitrodienes and amine derivatives were stirred in dichloromethane until completion of the reaction. Chloroform was added to the reaction mixture. The organic layer was separated and washed with water (4 × 30 ml) and dried with $CaCl_2$ or $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel.

N-[1-(2-furanylmethanethio)-2-nitro-3,4,4-trichloro-1,3-butadienyl)]-N^1-phenyl Piperazine (7a)

Yield, 0.142 g (52%). m.p. 129–130°C. $R_f = 0.227$ ($CHCl_3$). IR (KBr): $\upsilon = 2850, 2930, 3100\ cm^{-1}$ (C—H), 1600 (C=C), 1285, 1540 (C—NO_2).$-^1H$ NMR($CDCl_3$, TMS int.): $\delta = 3.2–4.0$ ppm (m, 8H, $H_{piper.}$), 4.1–4.5 (m, 2H, S—CH_2), 6.2–7.6 (m, 8H, $H_{arom.}$). $C_{19}H_{18}SN_3Cl_3O_3$ (474.797) Calcd.: C, 48.06; H, 3.82; N, 8.85. Found: C, 47.34; H, 4.04; N, 7.94. MS m/z 475.

N-[1-(4-methoxyphenylthio)-2-nitro-3,4,4-trichloro-1,3-butadienyl)]-N¹-phenyl Piperazine (7b)

Yield, 0.168 g (63%). m.p. 181–182°C. $R_f = 0.280$ ($CHCl_3$). IR (KBr): $\nu = 2850, 2900, 3100\ cm^{-1}$ (C—H), 1600(C=C), 1275, 1530 (C—NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): δ = 2.8–3.1 ppm (m, 3H, OCH_3), 3.5–4.0 (m, 8H, $H_{piper.}$), 6.7–7.5 (m, 9H, $H_{arom.}$). $C_{21}H_{20}SN_3Cl_3O_3$ (500.836) Calcd. C, 50.36; H, 4.025; N, 8.39. Found: C, 49.50; H, 3.68; N, 8.27. MS m/z 501.

N-[1-(4-methoxyphenylthio)-2-nitro-3,4,4-trichloro-1,3-butadienyl)]-N¹-methyl Piperazine (7c)

Yield, 0.181 g (77%). m.p. 233–234°C. $R_f = 0.280$ (EtAc). IR (KBr): ν = 2750, 2850, 2900, 3020 cm^{-1} (C—H), 1590 (C=C), 1290, 1540 (C—NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): $\delta = 2.1–2.4$ ppm (m, 6H, $2CH_3$), 3.4–4.0 (m, 8H, $H_{piper.}$), 6.9–7.5 (m, 4H, $H_{arom.}$). $C_{16}H_{18}SN_3Cl_3O_3$ (438.762) Calcd.: C, 43.80; H, 4.13; N, 9.57. Found: C, 43.61; H, 4.21; N, 9.25. MS m/z 438.9.

N-[1-(4-methoxyphenylthio)-2-nitro-3,4,4-trichloro-1,3-butadienyl)]-N¹-ethoxycarbonyl Piperazine (7d)

Yield, 0.208 g (78%). m.p. 165–166°C. R_f = 0.814 (EtAc). IR (KBr): ν = 2850, 2900, 3050, 3100 cm^{-1} (C—H), 1580 (C=C), 1250, 1280, 1530 (C—NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): $\delta = 2.9–3.6$ ppm (m, 8H, $H_{piper.}$), 3.7–3.9 (m, 3H, $-OCH_3$), 4.0–4.4 (m, 5H, OCH_2—CH_3), 6.8–7.6 (m, 4H, $H_{arom.}$). $C_{18}H_{20}SN_3Cl_3O_5$ (496.801) Calcd.: C, 43.52; H, 4.05; N, 8.46. Found: C, 43.53; H, 3.96; N, 9.04. MS m/z 496.9.

N-[1-(4-methoxyphenylthio)-2-nitro-3,4,4-trichloro-1,3-butadienyl)]-N¹-[4-fluorophenyl]-piperazine (7e)

Yield, 0.145 g (52%). m.p. 156–157°C. $R_f = 0.777$ ($CHCl_3$). IR (KBr): ν = 2830, 2950, 3010 cm^{-1} (C—H), 1595 (C=C), 1215, 1240, 1510 (C—NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): $\delta = 2.6–3.0$ ppm (m, 3H, OCH_3), 3.4–4.0 (m, 8H, $H_{piper.}$), 6.6–7.5 (m, 8H, $H_{arom.}$). $C_{21}H_{19}SN_3Cl_3O_3F$ (518.824) Calcd.: C, 48.61; H, 3.69; N, 8.09. Found: C, 48.86; H, 3.48; N, 7.72. MS m/z 519.

1-(4-Methoxyphenylthio)-2-nitro-3,4,4-trichloro-1-(4-morpholino)-1,3-butadiene (9a)

Yield, 0.145 g (63%). m.p. 133–134°C. R_f = 0.294 ($CHCl_3$). IR (KBr): ν = 2820, 2980, 3030 cm^{-1} (C—H, 1595 (C=C), 1230, 1280, 1545 (C—NO_2). –1H NMR($CDCl_3$, TMS int.): δ = 1.0–1.5 ppm (m, 4H, $N(CH_2)_2$), 3.0–3.6 (m, 4H, $O(CH_2)_2$), 3.7–3.9 (m, 3H, OCH_3), 6.8–7.4 (m, 4H, $H_{arom.}$). $C_{15}H_{15}SN_2Cl_3O_4$ (425.722) Calcd.: C, 42.32; H, 3.55; N, 6.58. Found: C, 43.09; H, 3.68; N, 6.36.

1-(4-Methoxyphenylthio)-2-nitro-3,4,4-trichloro-1-(piperidino)-1,3-butadiene (11a)

Yield, 0.122 g) 54%). m.p. 125–126°C. $R_F = 0.353$ ($CHCl_3$). IR (KBr): $\nu = 2835$, 2950 cm^{-1} (C—H), 1595 (C=C), 1220, 1260, 1540 (C—NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): $\delta = 0.8$–2.2 ppm (m, 6H, $(CH_2)_3$), 2.9–3.8 (m, 4h, $N(CH_2)_2$), 3.8–4.0 (m, 3H OCH_3), 6.8–7.6 (m, 4H, $H_{arom.}$). $C_{16}H_{17}SN_2Cl_3O_3$ (423.747) Calcd.: C, 45.35; H, 4.04; N, 6.61. Found: C, 45.42; H, 3.68; N, 6.73.

N,N[1]-[1-(4-methoxyphenylthio)-2-nitro-3,4,4-trichloro-1,3-butadienyl)]-homopiperazine (13a)

Yield, 0.141 g (34%). m.p. 158–159°C. $R_f = 0.812$ (EtAc/$CHCl_3$ 1:1). —IR (KBr): $\nu = 2850$, 3010 cm^{-1} (C—H), 1580 (C=C), 1240, 1535 (C—NO_2). $-^1H$ NMR($CDCl_3$, TMS int.): $\delta = 0.7$–1.9 ppm (m, 10H, $H_{homopip.}$), 3.4–3.9 (m, 6H, 2 OCH_3), 6.8–7.4 (m, 8H, $h_{arom.}$). $C_{27}H_{24}S_2N_4Cl_6O_6$ (777.362) Calcd.: C, 39.71; H, 3.11; N, 7.20. Found: C, 39.46; H, 3.18; N, 6.50.

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