New NO-Donors with Antithrombotic and Vasodilating Activities, IX[2]:

Thiadiazole Nitrosimines

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Twenty 1,3,4-thiadiazole-2-nitrosimines and two 1,2,4-thiadiazole-5-nitrosimines were synthesized and assayed in the *Born*-test for their antiplatelet activity. Only two 1,3,4-thiadiazoles inhibited the aggregation at $IC_{50} < 10$ µmol/L. In an *in vivo* thrombosis model only in arterioles a small inhibition of thrombus formation was observed. The poor test results correspond to a very high chemical stability of the titel nitrosimines.

Neue NO-Pharmaka mit antithrombotischen und gefäßerweiternden Eigenschaften, 9. Mitt.[2]:
Thiadiazolnitrosimine

Zwanzig 1,3,4-Thiadiazol-2-nitrosimine und zwei 1,2,4-Thiadiazol-5-nitrosimine wurden dargestellt und im *Born*-Test bezüglich ihrer Hemmwirkung auf die Thrombozytenaggregation geprüft. Nur zwei 1,3,4-Thiadiazole hemmten die durch Collagen ausgelöste Aggregation in Konzentrationen < 10 µmol/L halbmaximal. In einem *in vivo* Thrombosemodell wurde nur in Arteriolen eine geringe Hemmung der Thrombusbildung beobachtet. Diese Ergebnisse entsprechen der auffallenden chemischen Stabilität dieser Nitrosimine.

Recently we reported on the *in vitro* antiplatelet activity and the *in vivo* antithrombotic effects of thiazole- and 1,3-benzothiazole nitrosimines[1,2]. Both effects are based on the cleavage of the nitrosimino group whereby an active metabolite presumable a NO species is formed. We now have investigated the influence of a second N-atom in the thiazole ring system. This replacement leads to the 1,2,4-thiadiazole-5-nitrosimines or 1,3,4-thiazole-2-nitrosimines, respectively.

The synthetic routes to the title compounds are compiled in Scheme 1. The most convenient method for 1,3,4-thiadiazole-2-amines was found by *Weidinger*[3]. By *Pinner* reaction of nitriles the corresponding iminoether hydrochlorides were obtained. Cyclisation with thiosemicarbazide afforded thiadiazole-2-amines which were subsequently alkylated at the sp^2-amidine N, and by applying *Lüdtke's*[1] superior two phase nitrosation method **1-20** were obtained in good yields.

The synthesis of the 1,2,4-thiadiazole **21** was performed by the method of *Goerdeler*[4]: Amidines are treated with bromine and cyclized with thiocyanates. The resulting 1,2,4-thiadiazole-5-amine then was alkylated and nitrosated as usual[1,2]. The oxidative dimerisation of *N*-aryl-thioureas was found by *Hector*[5,6] and gives 1,2,4-thiazole-3,5-diimines. The nitrosimine **22** was obtained by nitrosation in 28% yield.

The most striking feature of **1-20** is the existence of *Z*/*E*-isomers (NMR spectra) which we have discussed in detail lately[7]. The mass spectra mostly give rise to molecular ions of high intensity. This underlines the high stability of the compound even when an unpaired electron is present. The infrared spectra show a characteristic double absorption about 1400 cm^{-1} which represents the N-NO vibration.

The antiplatelet properties of **1-20** are compiled in Tab. 1 and in Scheme 2, respectively. The first compound we had prepared was the most simple 3-methyl derivative **1**. An IC_{50} = 7.5 µmol/l appeared promising. It was disappointing that this result already marked the peak activity in this series. In contrast to the thiazole and benzothiazole series where lipophilic substitution in 3-position was favorable, all our attempts to improve the activity of **1** were in vain. When the methyl group in **1** was replaced by other hydrocarbon groups (cf. **2-4**) the activity was bisected. The introduction of an additional methyl group in 5-position gave a further decay of the antiplatelet effect as comparison of the pairs **1** and **5** or **2** and **6** clearly shows. Substituents in 3-position, which contain double bonds had been useful in the thiazole series. In the thiadiazoles it's just the other way round. Compounds **7-9** developed no activity at all. When the substituent in 5-position was changed to ethyl, compound **10** exhibited an activity equivalent to **1**. Comparison of **2** with **11** makes clear that this cannot be generalized. An aromatic ring in 5-position generally decreased the activity. This is underlined by comparison of the pairs **1/12**, **2/13**, **3/14**, and **4/15**.

Among the bisnitrosimines two compounds with medium activity (**17**, **20**) were obtained; among the 1,2,4-thiazoles (**21**, **22**) no antiplatelet effects were observed.

One has to bear in mind that *in vitro* the cleavage of the N-NO bond of nitrosimines is supported by visible light. As in the body nearly no light is present this function has to be taken over by enzymes. We, therefore, submitted compounds **12** and **20** to an *in vivo* thrombosis model. Two h after oral administration of 60 mg/kg to rats, only in arterioles a slight but significant inhibition of thrombus forma-

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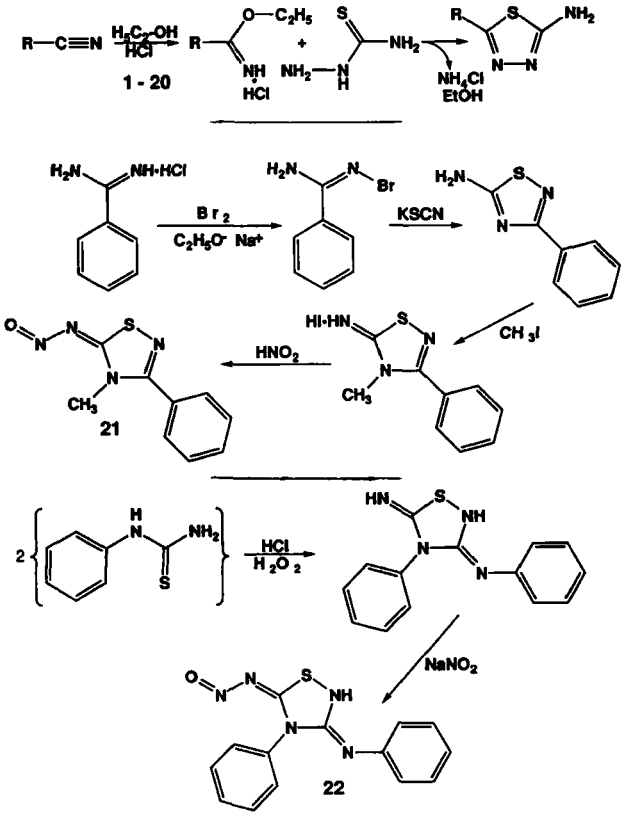
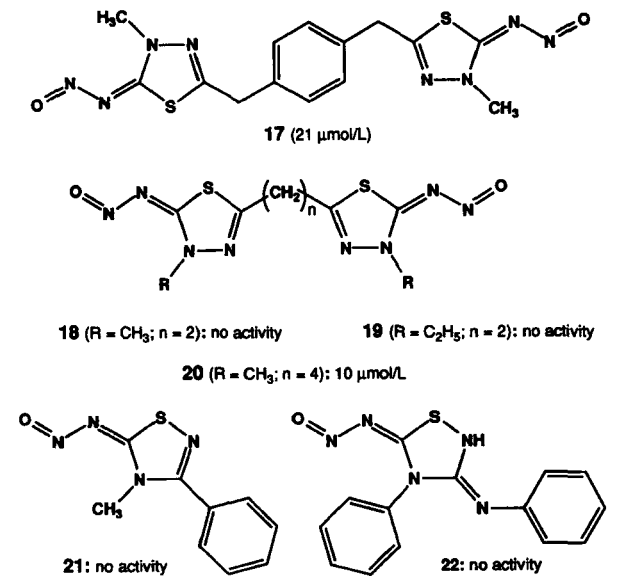


Scheme 1: Synthetic routes to 1,2,4- and 1,3,4-thiadiazole nitrosimines

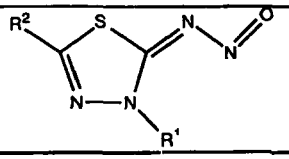


Scheme 2: Antiplatelet effects of bis-1,3,4-thiadiazole-2-nitrosimines **17**, **20** and 1,2,4-thiadiazole-5-nitrosimines

tion was observed (**12**: 14 ± 9%, $p \geq 0.2$; **20**: 9 ± 5%, $p \geq 0.002$).

In general we conclude that the introduction of a second N-atom into the thiazole ring at either position stabilizes the nitrosoiminino group against degradation by visible light *in vitro*. This stabilization seems to occur as well *in vivo*.

Table 1: Effect of 1,3,4-thiadiazole-2-nitrosimines on the platelet aggregation induced by collagen in the Born-test (n.a. = no activity)



Compound	R^1	R^2	IC_{50} [µmol/L]
1	CH_3	H	7.5
2	C_2H_5	H	16
3	C_3H_7	H	16
4	C_4H_9	H	19
5	CH_3	CH_3	30
6	C_2H_5	CH_3	40
7	allyl	CH_3	n.a.
8	2-propinyl	CH_3	n.a.
9	3-phenyl-2-butenyl	CH_3	n.a.
10	CH_3	C_2H_5	7.5
11	C_2H_5	C_2H_5	33
12	CH_3	phenyl	12
13	C_2H_5	phenyl	27
14	C_3H_7	phenyl	43
15	C_4H_9	phenyl	41
16	2-propinyl	phenyl	67

Experimental Part

The synthesis of the imines was performed with published methods[3-6]. - For nitrosation the two-phase ($CHCl_3/H_2O$) nitrosation was applied[1]. - Spectroscopical devices and pharmacological test systems have been communicated recently[8].- IR spectra were obtained in KBr, ^{1}H-NMR spectra were run in [D_6]DMSO at 300 MHz.- Temp. in °C.

3-Methyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine (**1**)

Yellow crystals[9] (isopropanol), mp. 117° (decompn.). Yield 62%.- $C_3H_4N_4OS$ (144.2) Calcd. C 25.0 H 2.80 N 38.9 Found C 25.1 H 2.77 N 39.2.- IR: 3065; 1747; 1490; 1466; 1396; 1357; 1286; 1255; 1232; 1172; 1124; 1076; 958; 874; 845; 824; 715; 664 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 212 (3.89), 320 (4.02), 448 nm (1.59).- ^{1}H-NMR: δ (ppm) = 9.07 (s, 1H, 5-H), 4.01 (bs, 3H, 3-CH_3).- MS (65°): m/z = 144 (83%, $M^{+\cdot}$), 114 (24), 100 (32), 73 (58), 72 (12), 56 (16), 55 (20), 46 (18), 45 (73), 43 (100).

3-Ethyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine (**2**)

Yellow orange crystals (isopropanol), mp. 127°. Yield 82%.- $C_4H_6N_4OS$ (158.2) Calcd. C 30.4 H 3.82 N 35.4 Found C 30.7 H 3.83 N 35.6.- IR: 3437; 3054; 2970; 2932; 2873; 2707; 1729; 1671; 1518; 1495; 1443; 1408; 1359; 1308; 1265; 1244; 1189; 1113; 1082; 984; 937; 868; 842; 783; 684; 655 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 204 (3.99), 212 (4.00), 320 (3.85), 448 nm (1.69).- ^{1}H-NMR: δ (ppm) = 9.11 (s, 1H, 5-H), 4.45 (bs, 2H, 3-CH_2), 1.41 (t, J = 7 Hz, 3H, CH_3).- MS (100°): m/z = 158 (54%, $M^{+\cdot}$), 130 (93), 115 (22), 103 (18), 87 (46), 77 (13), 72 (19), 70 (50), 69 (34), 60 (15), 59 (32), 55 (88), 45 (100).

N-Nitroso-3-propyl-1,3,4-thiadiazole-2(3H)-imine (**3**)

Yellow orange crystals (isopropanol), mp. 109°. Yield 70%.- $C_5H_8N_4OS$ (172.2) Calcd. C 34.9 H 4.68 N 32.5 Found C 34.9 H 4.75 N 32.3.- IR:

3054; 2964; 2875; 1724; 1519; 1495; 1463; 1437; 1412; 1362; 1310; 1267; 1240; 1185; 1106; 1088; 1032; 962; 900; 866; 843; 748; 702; 658; 623 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 210 (4.04), 320 (3.99), 448 nm (1.65).- ^{1}H-NMR: δ (ppm) = 9.10 (s, 1H, 5-H), 4.38 (bs, 2H, 3-CH_2), 1.86 (m, J = 7/7 Hz, 2H, C$\underline{H}_2$-CH_3), 0.88 (t, J = 7 Hz, 3H, CH_3).- MS (40°): m/z = 172 (52%, $M^{+\cdot}$), 144 (53), 142 (12), 129 (20), 115 (25), 103 (100), 102 (30), 101 (24), 100 (33), 87 (16), 84 (22), 56 (19), 55 (79), 45 (31), 43 (48), 41 (32).

3-Butyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine (**4**)

Yellow orange plates (ligroin), mp. 55°. Yield 43%.- $C_6H_{10}N_4OS$ (186.2) Calcd. C 38.7 H 5.41 N 30.1 Found C 39.1 H 5.62 N 30.5.- IR: 3443; 3054; 2955; 2929; 2870; 1520; 1499; 1462; 1418; 1359; 1305; 1251; 1170; 1090; 961; 923; 848; 699; 622 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 9.10 (s, 1H, 5-H), 4.41 (bs, 2H, 3-CH_2, 1.86 (tt, 2H, 3-CH_2-C$\underline{H}_2$), 1.27 (m, 2H, C$\underline{H}_2$-CH_3), 0.90 (t, J = 7.2 Hz, 3H, CH_3).- MS (100°): m/z = 186 (48%, $M^{+\cdot}$), 156 (25), 141 (10), 114 (63), 102 (62), 101 (58), 100 (66), 87 (48), 74 (10), 73 (24), 72 (10), 57 (39), 56 (16), 55 (63), 45 (48), 43 (35), 42 (12), 41 (100), 39 (23).

3,5-Dimethyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine (**5**)

Orange needles (isopropanol), mp. 118°. Yield 64%.- $C_4H_6N_4OS$ (158.2) Calcd. C 30.4 H 3.82 N 35.4 Found C 30.6 H 3.84 N 35.2.- IR: 3423; 2966; 2920; 2592; 1547; 1535; 1427; 1383; 1361; 1288; 1236; 1212; 1195; 1108; 1057; 1002; 955; 840; 711; 673; 639 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 210 (4.30), 346 (3.98), 468 nm (1.55).- ^{1}H-NMR: δ (ppm) = 3.94 (bs, 3H, 3-CH_3), 2.51 (s, 3H, 5-CH_3).- MS (50°): m/z = 158 (33%, $M^{+\cdot}$), 130 (3), 128 (12), 114 (12), 73 (74), 72 (16), 70 (13), 69 (22), 59 (100), 58 (15), 46 (18), 45 (12), 43 (88), 42 (37), 41 (16), 30 (29).

3-Ethyl-5-methyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine (**6**)

Orange crystals (isopropanol), mp. 71°. Yield 79%.- $C_5H_8N_4OS$ (172.2) Calcd. C 34.9 H 4.68 N 32.5 Found C 34.8 H 4.61 N 32.3.- IR: 3417; 2973; 2933; 2873; 1626; 1545; 1525; 1449; 1429; 1407; 1384; 1358; 1344; 1292; 1206; 1192; 1090; 1068; 1015; 977; 923; 840; 791; 668; 651; 634 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 210 (4.34), 346 (3.97), 468 nm (1.81).- ^{1}H-NMR: δ (ppm) = 4.36 (bs, 2H, 3-CH_2), 2.63 (s, 3H, 5-CH_3), 1.38 (t, J = 7 Hz, 3H, CH_2-C$\underline{H}_3$).- MS (40°): m/z = 172 (41%, $M^{+\cdot}$), 144 (3), 142 (3), 128 (12), 101 (21), 87 (21), 59 (100), 42 (43).

3-Allyl-5-methyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine (**7**)

Orange crystals (isopropanol), mp. 48°. Yield 76%.- $C_6H_8N_4OS$ (184.2) Calcd. C 39.1 H 4.38 N 30.4 Found C 38.9 H 4.33 N 30.5.- IR: 3424; 2984; 2926; 1644; 1552; 1528; 1468; 1421; 1383; 1354; 1279; 1262; 1211; 1171; 1142; 1052; 995; 943; 926; 835; 713; 635 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 210 (4.04), 324 (3.98), 448 nm (1.68).- ^{1}H-NMR: δ (ppm) = 5.98 (m, 1H, C$\underline{H}$=CH_2), 5.29 (d, J = 10 Hz, 2H, *trans* CH=C$\underline{H}_2$), 5.22 (d, J = 17 Hz, 1H, *cis* CH=C$\underline{H}_2$), 4.97 (bs, 2H, 3-CH_2), 2.63 (s, 3H, 5-CH_3).- MS (40°): m/z = 184 (11%, $M^{+\cdot}$), 156 (6), 154 (64), 139 (19), 113 (16), 99 (12), 86 (35), 72 (15), 69 (42), 59 (97), 41 (100), 39 (40), 28 (17).

5-Methyl-N-nitroso-3-(2-propinyl)-1,3,4-thiadiazole-2(3H)-imine (**8**)

Orange crystals (isopropanol), mp. 84°. Yield 89%.- $C_6H_6N_4OS$ (182.2) Calcd. C 39.6 H 3.32 N 30.8 Found C 39.3 H 3.13 N 30.5.- IR: 3257; 2978; 2924; 2125; 1656; 1560; 1533; 1467; 1431; 1407; 1381; 1360; 1274; 1249; 1206; 1140; 1056; 992; 913; 836; 718; 692; 658; 634; 616 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 214 (3.99), 324 (4.01), 454 nm (1.70).- ^{1}H-NMR: δ (ppm) = 5.20 (bs, 2H, 3-CH_2), 3.60 (s, 1H, ≡CH), 2.65 (s, 3H, 5-CH_3).- MS (80°): m/z = 182 (5%, $M^{+\cdot}$), 99 (28), 97 (16), 84 (25), 72 (12), 59 (100), 52 (11), 42 (17), 39 (74), 30 (16).

[E]-5-Methyl-N-nitroso-3-(3-phenyl-2-propenyl)-1,3,4-thiadiazole-2(3H)-imine (**9**)

Orange needles (isopropanol), mp. 80°. Yield 52%.- $C_{12}H_{12}N_4OS$ (260.3) Calcd. C 55.4 H 4.65 N 21.5 Found C 55.3 H 4.62 N 21.6.- IR: 3425; 3050; 3018; 2925; 1540; 1526; 1494; 1415; 1403; 1382; 1348; 1281; 1255; 1209; 1137; 1062; 1025; 1007; 976; 963; 931; 836; 743; 686; 638 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.47), 250 (4.26), 324 (3.96), 454 nm (1.64).- ^{1}H-NMR: δ (ppm) = 7.48 (d, J = 7 Hz, 2H, pH-2-H and 6-H), 7.31 (m, 3H, ph-3-H, 4-H, 5-H), 6.71 (d, J = 17 Hz, 1H, =CH-ph), 6.44 (dt, J = 17/7 Hz, 1H, 3-CH_2-C$\underline{H}$=), 5.13 (bs, 2H, 3-CH_2), 2.51 (s, 3H, 5-CH_3).- MS (180°): m/z = 260 (5%, $M^{+\cdot}$), 232 (4), 230 (23), 118 (10), 117 (100), 116 (11), 115 (40), 91 (67), 77 (11), 59 (18), 51 (10), 39 (14).

5-Ethyl-3-methyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine (**10**)

Orange crystals (isopropanol), mp. 57°. Yield 48%.- $C_5H_8N_4OS$ (172.2) Calcd. C 34.9 H 4.68 N 32.5 Found C 35.1 H 4.79 N 32.6.- IR: 3423; 2970; 2929; 1543; 1451; 1425; 1388; 1363; 1309; 1262; 1228; 1193; 1090; 1067; 1036; 969; 933; 837; 797; 676; 636 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 210 (3.45), 326 (3.58), 448 nm (1.34).- ^{1}H-NMR: δ (ppm) = 3.94 (bs, 3H, 3-CH_3), 2.98 (q, J = 7.4 Hz, 2H, 5-CH_2), 1.30 (t, J = 7.4 Hz, 3H, CH_2-C$\underline{H}_3$).- MS (100°): m/z = 172 (28%, $M^{+\cdot}$), 144 (13), 84 (22), 83 (35), 73 (100), 72 (10), 56 (15), 45 (26), 43 (64), 41 (14), 39 (13), 36 (27), 30 (18).

3,5-Diethyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine (**11**)

Orange oil. Yield 56%.- $C_6H_{10}N_4OS$ (186.2) Calcd. C 38.7 H 5.41 N 30.1 Found C 39.0 H 5.57 N 30.1.- IR: 3312; 2972; 2932; 2874; 1672; 1596; 1562; 1533; 1443; 1421; 1359; 1297; 1266; 1191; 1057; 984; 930; 906; 834; 788; 711 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 210 (3.45), 326 (3.68), 448 nm (1.34).- ^{1}H-NMR: δ (ppm) = 4.36 (bs, 2H, 3-CH_2), 2.98 (q, J = 7.4 Hz, 2H, 5-CH_2), 1.38 (t, J = 7.4 Hz, 3H, 3-CH_2-C$\underline{H}_3$), 1.30 (t, J = 7.4 Hz, 3H, 5-CH_2-C$\underline{H}_3$).- MS (40°): m/z = 186 (52%, $M^{+\cdot}$), 156 (7), 129 (18), 115 (14), 97 (11), 87 (36), 83 (27), 73 (79), 59 (39), 56 (36), 45 (43), 41 (59), 39 (21), 29 (100).

3-Methyl-N-nitroso-5-phenyl-1,3,4-thiadiazole-2(3H)-imine (**12**)

Orange crystals (isopropanol), mp. 142°. Yield 68%.- $C_9H_8N_4OS$ (220.3) Calcd. C 49.1 H 3.66 N 25.4 Found C 48.8 H 3.58 N 25.3.- IR: 3423; 3016; 1540; 1510; 1483; 1445; 1426; 1384; 1368; 1300; 1232; 1204; 1099; 1079; 1052; 1027; 998; 940; 926; 837; 770; 723; 691; 614 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.33), 270 (3.82), 342 (4.08), 448 nm (1.76).- ^{1}H-NMR/300 MHz ([D_6]DMSO): δ (ppm) = 7.97 (d, J = 7 Hz, 2H, ph-2-H, 6-H), 7.61 (m, 3H, ph-3-H, 4-H, 5-H), 4.07 (bs, 3H, 3-CH_3).- MS (100°): m/z = 220 (22%, $M^{+\cdot}$), 192 (5), 163 (39), 132 (48), 121 (100), 104 (27), 77 (50), 73 (76), 51 (26), 43 (30), 30 (17).

3-Ethyl-N-nitroso-5-phenyl-1,3,4-thiadiazole-2(3H)-imine (**13**)

Orange needles (isopropanol), mp. 128°. Yield 61%.- $C_{10}H_{10}N_4OS$ (234.3) Calcd. C 51.3 H 4.30 N 23.9 Found C 51.2 H 4.28 N 24.0.- IR: 3430; 2984; 2932; 1641; 1567; 1534; 1515; 1474; 1458; 1424; 1395; 1359; 1342; 1319; 1300; 1296; 1266; 1254; 1232; 1205; 1186; 1138; 1117; 1098; 1066; 1025; 1002; 987; 925; 878; 854; 805; 772; 731; 655 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 204 (4.36), 270 (3.87), 342 (4.15), 450 nm (1.86).- ^{1}H-NMR: δ (ppm) = 7.97 (d, J = 7.5 Hz, 2H, ph-2-H, 6-H), 7.67-7.57 (m, 3H, ph-3-H, 4-H, 5-H), 4.50 (bs, 2H, 3-CH_2), 1.48 (t, J = 7.2 Hz, 3H, CH_2-C$\underline{H}_3$).- MS (110°): m/z = 234 (37%, $M^{+\cdot}$), 206 (11), 204 (5), 190 (20), 177 (44), 162 (17), 146 (22), 131 (34), 121 (100), 104 (31), 87 (29), 77 (45), 59 (18), 51 (17), 42 (15), 29 (37).

N-Nitroso-5-phenyl-3-propyl-1,3,4-thiadiazole-2(3H)-imine (**14**)

Orange crystals (isopropanol), mp. 109°. Yield 79%.- $C_{11}H_{12}N_4OS$ (248.3) Calcd. C 53.2 H 4.87 N 22.6 Found C 53.0 H 4.77 N 22.5.- IR:

3043; 2963; 2935; 2878; 1532; 1482; 1466; 1453; 1436; 1413; 1359; 1316; 1297; 1266; 1194; 1155; 1107; 1079; 1028; 1010; 939; 895; 840; 769; 719; 693; 651; 616; 605 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.34), 294 (3.92), 440 nm (1.77).- ^{1}H-NMR: δ (ppm) = 7.97 (d, J = 7 Hz, 2H, ph-2-H, 6-H), 7.61 (m, 3H, ph-3-H, 4-H, 5-H), 4.44 (bs, 2H, 3-CH_2), 1.93 (m, 2H, C<u>H</u>$_2$-CH_3), 0.94 (t, J = 7 Hz, 3H, CH_3).- MS (40°): m/z = 248 (10%, $M^{+\cdot}$), 220 (70), 218 (7), 178 (30), 131 (100), 121 (71), 118 (12), 104 (84), 77 (56), 51 (21), 43 (22).

3-Butyl-N-nitroso-5-phenyl-1,3,4-thiadiazole-2(3H)-imine (**15**)

Orange crystals (isopropanol), mp. 85°. Yield 68%.- $C_{12}H_{14}N_4OS$ (262.3) Calcd. C 54.9 H 5.38 N 21.4 Found C 54.8 H 5.36 N 21.3.- IR: 3047; 3027; 2949; 2875; 1579; 1480; 1438; 1410; 1354; 1300; 1263; 1241; 1185; 1078; 1024; 1011; 920; 840; 785; 717; 689; 601 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 204 (4.24), 318 (3.75), 448 nm (1.80).- ^{1}H-NMR: δ (ppm) = 7.97 (d, J = 7 Hz, 2H, ph-2-H, 6-H), 7.61 (m, 3H, ph-3-H, 4-H, 5-H), 4.47 (bs, 2H, 3-CH_2), 1.89 (tt, J = 7/7 Hz, 2H, 3-CH_2-C<u>H</u>$_2$), 1.37 (m, 2H, C<u>H</u>$_2$-CH_3), 0.93 (t, J = 7 Hz, 3H, CH_3).- MS (80°): m/z = 262 (29%, $M^{+\cdot}$), 234 (28), 232 (19), 190 (10), 178 (32), 176 (22), 163 (12), 132 (10), 131 (65), 121 (100), 104 (79), 103 (12), 98 (28), 77 (49), 73 (11), 57 (15), 51 (13), 43 (15), 41 (37).

N-Nitroso-5-phenyl-3-(2-propinyl)-1,3,4-thiadiazole-2(3H)-imine (**16**)

Orange needles (isopropanol), mp. 142°. Yield 62%.- $C_{11}H_8N_4OS \cdot {}^1/_4 H_2O$ (248.8) Calcd. C 53.1 H 3.34 N 22.5 Found C 53.2 H 3.27 N 22.1.- IR: 3138; 3057; 2154; 1567; 1531; 1480; 1457; 1381; 1323; 1304; 1254; 1179; 1144; 1104; 1070; 1009; 962; 915; 804; 761; 726; 712; 690; 638 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 204 (4.36), 278 (3.94), 348 nm (3.78).- ^{1}H-NMR: δ (ppm) = 7.99 (d, J = 7 Hz, 2H, ph-2-H, 6-H), 7.64 (m, 3H, ph-3-H and H-5), 5.34 (bs, 2H, 3-CH_2), 3.67 (s, 1H, ≡CH).- MS (120°): m/z = 244 (10%, $M^{+\cdot}$), 216 (39), 214 (39), 161 (32), 128 (30), 121 (100), 103 (28), 97 (12), 79 (12), 77 (39), 51 (18), 39 (29).

5,5'-p-Xylylene-bis-[3-methyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine (**17**)

Yellow orange crystals (ethanol), mp. 142°. Yield 17%.- $C_{14}H_{14}N_8O_2S_2$ (390.4) Calcd. C 43.1 H 3.61 N 28.7 Found C 43.7 H 3.71 N 28.2.- IR: 3432; 3022; 2942; 1631; 1537; 1507; 1484; 1433; 1387; 1363; 1277; 1236; 1195; 1140; 1107; 1057; 981; 965; 838; 768; 725; 718; 638; 658; 635 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 198 (4.65), 326 (4.28), 450 nm (2.05).- ^{1}H-NMR: δ (ppm) = 7.41 (s, 4H, p-ph), 4.37 (s, 4H, C<u>H</u>$_2$-ph-C<u>H</u>$_2$), 3.96 (bs, 6H, 3 and 3'CH_3).- MS (100°): m/z = 390 (2%, $M^{+\cdot}$), 335 (14), 334 (70), 245 (11), 231 (14), 220 (14); 219 (100), 147 (27), 145 (15), 134 (14), 130 (50), 129 (20), 116 (15), 115 (20), 104 (35), 103 (24), 102 (10), 91 (15), 89 (13), 78 (12), 77 (18), 69 (37), 63 (12), 51 (11), 43 (54), 39 (11), 28 (66).

5,5'-Ethylene-bis-[3-methyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine] (**18**)

Yellow orange crystals (isopropanol), mp. 161° (decomp.). Yield 18%.- $C_8H_{10}N_8O_2S_2 \cdot {}^1/_8$ isopropanol (321.9) Calcd. C 31.2 H 3.44 N 34.8 Found C 30.8 H 3.44 N 34.2.- IR: 3435; 2919; 1579; 1523; 1486; 1429; 1391; 1362; 1313; 1284; 1239; 1206; 1139; 1112; 1072; 970; 839; 754; 716 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 216 (3.54), 326 (4.08), 450 nm (2.01).- ^{1}H-NMR: δ (ppm) = 4.00 (bs, 6H, 3 and 3'-CH_3), 3.48 (s, 4H, $(CH_2)_2$).- MS (100°): m/z = 314 (3%, $M^{+\cdot}$), 286 (31), 285 (18), 284 (17), 259 (13), 258 (76), 257 (100), 169 (53), 168 (12), 129 (21), 128 (34), 109 (37), 85 (26), 83 (42), 77 (11), 69 (15), 45 (19), 43 (12), 41 (12).

5,5'-Ethylene-bis-[3-ethyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine] (**19**)

Yellow orange crystals (isopropanol), mp. 152° (decomp.). Yield 32%.- $C_{10}H_{14}N_8O_2S_2 \cdot {}^1/_8$ isopropanol (349.9) Calcd. C 35.6 H 4.32 N 32.1 Found C 35.5 H 4.35 N 31.8.- IR: 3422; 2978; 2935; 1580; 1559; 1523; 1480; 1422; 1381; 1351; 1336; 1293; 1255; 1181; 1138; 1118; 1091; 1006; 939; 925; 838; 804; 755; 713; 670 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 216 (3.56), 326 (4.00), 450 nm (2.01).- ^{1}H-NMR: δ (ppm) = 4.37 (bs, 4H, 3 and 3'-CH_2), 3.49 (s, 4H, $CH_2)_2$), 1.35 (t, 6H, 3 and 3'-CH_2-C<u>H</u>$_3$).- MS (140°): m/z = 342 (5%, $M^{+\cdot}$), 314 (15), 286 (34), 257 (13), 184 (11), 183 (22), 168 (12), 156 (15), 143 (100), 142 (15), 114 (13), 108 (13), 98 (23), 87 (10), 83 (64), 81 (18), 72 (11), 71 (18), 61 (12), 59 (15), 58 (37), 55 (46), 54 (15), 45 (14), 42 (31), 41 (16).

5,5'-Butylene-bis-[3-methyl-N-nitroso-1,3,4-thiadiazole-2(3H)-imine] (**20**)

Yellow orange crystals (isopropanol), mp. 144° (decomp.). Yield 45%.- $C_{10}H_{14}N_8O_2S_2$ (342.4) Calcd. C 35.1 H 4.12 N 32.7 Found C 35.1 H 4.15 N 32.2.- IR: 3423; 2951; 2918; 2861; 1654; 1539; 1519; 1481; 1457; 1429; 1388; 1363; 1299; 1286; 1223; 1194; 1123; 1100; 1078; 1058; 1005; 971; 955; 903; 840; 741; 725; 690; 655; 637 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 216 (4.28), 326 (4.31), 452 nm (2.00).- ^{1}H-NMR: δ (ppm) = 3.94 (bs, 6H, 3 and 3'-CH_3), 3.02 (t, 4H, C<u>H</u>$_2$-$(CH_2)_2$-C<u>H</u>$_2$), 1.83 (bs, 4H, CH_2-(C<u>H</u>$_2)_2$-CH_2).- MS (150°): m/z = 342 (5%, $M^{+\cdot}$), 314 (20), 288 (11), 287 (17), 286 (100), 285 (26), 226 (54), 198 (18), 197 (74), 196 (16), 182 (30), 157 (25), 155 (19), 144 (32), 143 (67), 142 (37), 130 (18), 109 (12), 85 (16), 83 (25), 73 (13), 69 (16), 43 (30), 41 (14).

4-Methyl-N-nitroso-3-phenyl-1,2,4-thiadiazole-5(2H)-imine (**21**)

Yellow needles (isopropanol), mp. 177° (decomp.); ref.[4]: 178°. Yield 68%.- $C_9H_8N_4OS$ (220.3) Calcd. C 49.1 H 3.66 N 25.4 Found C 49.3 H 3.59 N 25.0.- IR: 3439; 1631; 1600; 1578; 1547; 1491; 1445; 1392; 1342; 1241; 1182; 1137; 1036; 1019; 824; 790; 750; 720; 693 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 206 (4.34), 226 (4.16), 316 (3.70), 426 nm (1.95).- ^{1}H-NMR: δ (ppm) = 7.76 (d, 2H, ph-2-H, 6-H), 7.64 (m, 3H, ph-3-H, 4-H, 5-H), 3.98 (s, 3H, 3-CH_3).- MS (200°): m/z = 220 (22%, $M^{+\cdot}$), 192 (3), 190 (4), 176 (7), 149 (12), 135 (10), 104 (11), 103 (15), 87 (100), 77 (20), 73 (49), 51 (13), 46 (51), 30 (10).

N-Nitroso-4-phenyl-3-phenylimino-1,2,4-thiadiazolidine-5-imine (**22**)

Yellow crystals (isopropanol), mp. 184°; ref.[5]: 179°. Yield 28%.- $C_{14}H_{11}N_5OS \cdot {}^1/_4 H_2O$ (301.8) Calcd. C 55.7 H 3.84 N 23.2 Found C 55.7 H 3.57 N 23.5.- IR: 3305; 3055; 1607; 1598; 1565; 1539; 1497; 1489; 1447; 1406; 1343; 1230; 1119; 1079; 1049; 1022; 939; 880; 807; 754; 719; 689; 656; 611 cm^{-1}.- UV (CH_3OH): λ max (log ε) = 252 (4.21), 354 nm (3.53).- ^{1}H-NMR: δ (ppm) = 8.90 (s, 1H, 2-H, exchange D_2O), 7.70 (s, 5H, 4-ph), 7.61 (d, 2H, 3=N-ph-2-H, 6-H), 7.31 (d/d, 2H, 3=N-ph-3-H, 5-H), 7.06 (d/d, 1H, 3=N-ph-4-H).- MS (250°): m/z = 297 (5%, $M^{+\cdot}$), 269 (37), 195 (43), 194 (61), 150 (17), 119 (19), 118 (100), 92 (16), 91 (53), 77 (54), 65 (19), 64 (17), 63 (11), 51 (21).

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