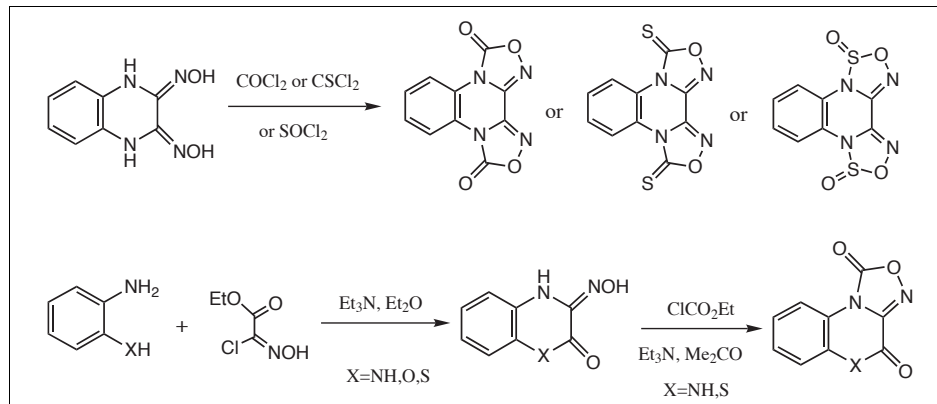


Konstantina C. Fylaktakidou^a, Konstantinos E. Litinas^b, Athanasios Saragliadis^b, Spyros G. Adamopoulos^b and Demetrios N. Nicolaides^{*b}

^aMolecular Biology and Genetics Department, Democritus University of Thrace, Alexandroupolis 68100, Greece

^bLaboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

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Bis-amidoxime **1** reacts with phosgene, thiophosgene and thionylchloride to give the corresponding bis-fused oxadiazolo- and oxathiadiazoloquinoxalines **2**, **4**, **5** along with the unexpected furazano-derivative **3**, while monoamidoximes **9**, **13** by treatment with ethyl chloroformate affords the oxadiazoloquinoxaline and the oxadiazolobenzothiazine derivatives **14**, **15** along with the dicarboxylated product **16**.

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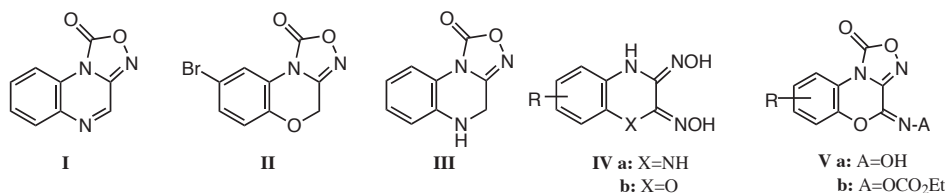
Introduction.

Numerous quinoxaline derivatives such as triazoloquinoxalines [1,2], ditriazoloquinoxalinediones [3], imidazoloquinoxalin-4-ones [4] have been synthesized and still attract the attention of many research groups, due to their biological importance [1-4]. 1*H*-[1,2,4]Oxadiazolo[4,3-*a*]quinoxalin-1-one (ODQ, **I**) [5,6] and 4*H*-8-bromo-[1,2,4]oxadiazolo[3,4-*d*]benzo[*b*][1,4]oxazin-1-one (NS2028, **II**) [6] appear to be potent and specific inhibitors of NO-stimulated soluble guanylyl cyclase activity in various cell types.

[1,2,4]Oxadiazolones are easily prepared, treating the appropriate amidoxime with ethyl chloroformate or phosgene [7]. Treatment of 2-oximino-1,2,3,4-tetrahydroquinoxaline (easily prepared from the reaction of *N*-cyanomethyl-*o*-phenylenediamine with hydroxylamine) with ethyl chloroformate gave 1-oxo-4,5-

dihydro[1,2,4]oxadiazolo[4,3-*a*]quinoxaline (**III**) in high yield [8].

In a previous paper [9] we reported the synthesis of some 2,3-bishydroxyimino-1,2,3,4-tetrahydroquinoxalines **IVa** and 2,3-bishydroxyimino-2,3-dihydro-4*H*-[1,4]benzoxazines **IVb** from the corresponding *o*-diamines or *o*-aminophenols and dicyan di-*N*-oxide. Also later it was studied [10] their reactions with ethyl chloroformate, in order to prepare the corresponding fused-oxadiazolones. Reflux of **IVa** in dry benzene with an excess of ethyl chloroformate led solely to the known [11,12] furazano-[3,4-*b*]quinoxalines in 17-28 % yield, while from **IVb** afforded the corresponding 4-hydroxyimino-1*H*,4*H*-[1,2,4]-oxadiazolo[3,4-*c*][1,4]benzoxazin-1-ones **Va**, the 4-ethoxycarbonyloxyimino- derivatives **Vb**, as well as the bis(ethoxycarbonyloxyimino)-derivatives of the starting bis-oximes **IV** [10]. In continuation here we report the syntheses of the title compounds depicted in Schemes 1,4.



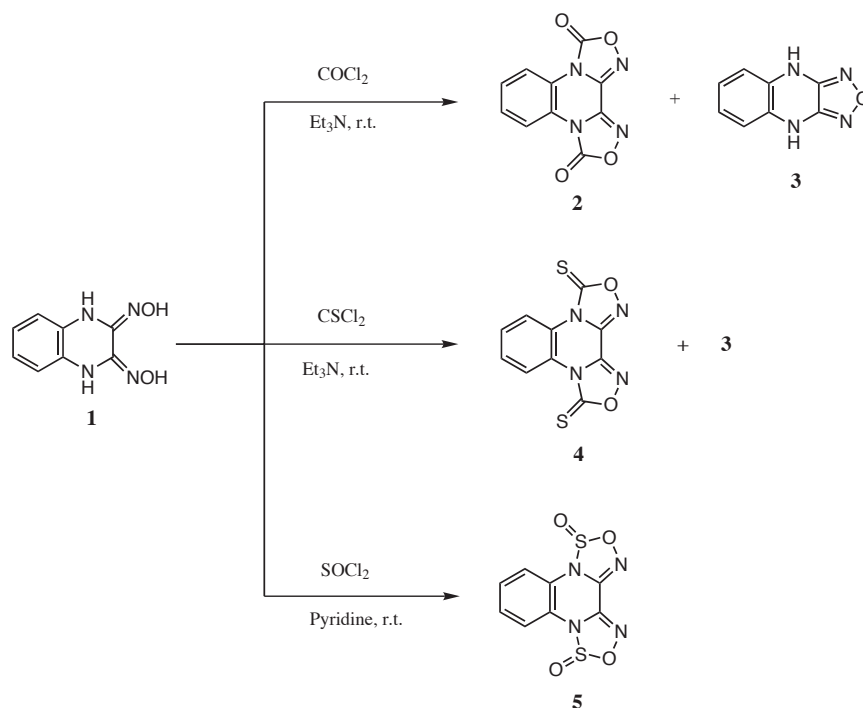
Results and Discussion.

Treatment of bis-amidoxime **1** [9] with excess of phosgene and triethylamine in dry dioxane at room temperature afforded the expected di[1,2,4]oxadiazolo-[4,3-*a*:3,4-*c*]quinoxaline-3,10-dione **2** in 33% yield and the known [13] 4,9-dihydrofurazano[3,4-*b*]quinoxaline **3** in 18% yield (Scheme 1).

oxadiazole ring followed by ring opening and elimination of COX can lead to the formation of product **3** obtained, as it is depicted in the mechanism proposed in Scheme 2.

We also studied similar reactions of 1,4-dihydro-2,3-quinoxalinedione 2-oxime **9**, as well as of 2*H*-[1,4]benzoxazine-2,3(4*H*)-dione 3-oxime **11** and 2*H*-[1,4]benzothiazine-2,3-(4*H*)-dione 3-oxime **13** in order to transform

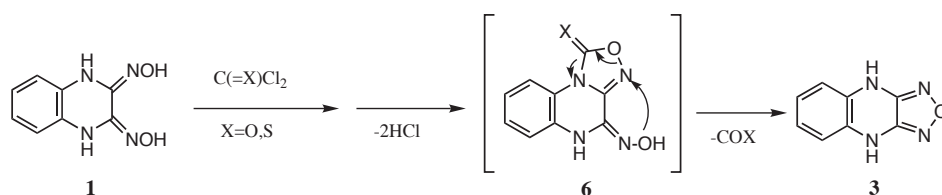
Scheme 1



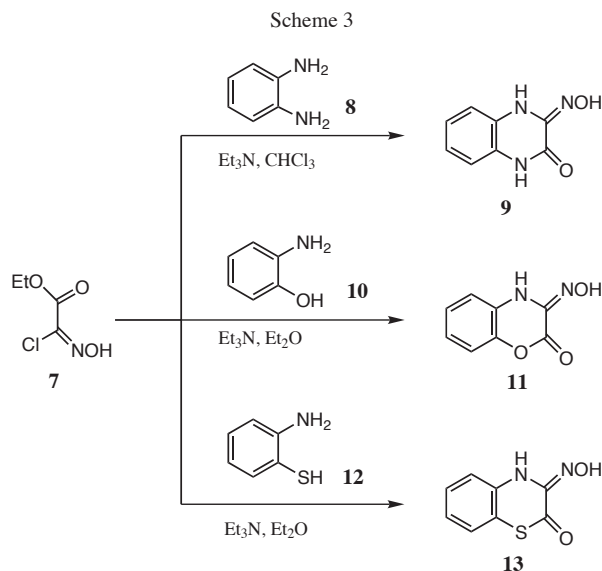
Following a similar procedure di[1,2,4]oxadiazolo[4,3-*a*:3,4-*c*]quinoxaline-3,10-dithione **4** was obtained in 31% yield along with compound **3** (18%) by treating compound **1** with two equivalents of thiophosgene [14]. Similarly, by treating compound **1** with thionyl chloride and pyridine [15] in dry THF, 1 λ^4 ,6 λ^4 -di[1,2,3,5]oxathia-diazolo[3,4-*a*:4,3-*c*]quinoxaline-1,6-dione **5** was obtained in 34% yield. Obviously products **2**, **4**, **5** were formed by a double lactamization of a bis(ethoxycarbonyloxyimino)-intermediate derivative of **1**, while compound **3** can be formed from the monolactamized intermediates **6**. Further intramolecular attack of the -OH group of **6** to its

their amidoxime moiety to the corresponding mono-fused systems. Several 4,4-dihydro-[1,2,4]triazoloquinoxaline-4-ones [16], 2,4-dihydro[1,2,4]triazolo[3,4-*c*][1,4]benzoxazines and -benzothiazines [17] show interesting biological and useful pharmacological properties. (Z)-Chloro-(hydroxyimino)acetic acid ethyl ester [18] reacted in the presence of triethylamine with *o*-phenylenediamine **8**, or with *o*-aminophenol **10** or with *o*-aminothiophenol **12** to give compounds **9**, **11**, **13** respectively in 87%, 83%, and 84% yield (Scheme 3). During the time that this work was in progress Csikos *et al.* [19] reported the syntheses, of 5,7-dichloro-, 6,8-dichloro-, 6-chloro-7-(trifluoromethyl)- and 7-chloro-6-(trifluoromethyl)-

Scheme 2



derivatives of **9**, following a similar treatment of the corresponding substituted 1,2-phenylenediamines with **7**.



When mono-amidoximes **9** and **13** were treated with ethyl chloroformate and triethylamine in acetone, the desired [1,2,4]oxadiazolo[4,3-*a*]quinoxaline-1,4(5*H*)-dione **14** and 4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzothiazine-1,4-dione **15** were obtained in 70% and 6% yield respectively. In the second reaction ethyl 3-[(ethoxycarbonyl)oxy]imino)-2-oxo-2*H*-1,4-benzothiazine-4-carboxylate **16** was derived also in 93 % yield.

Treatment of compound **11** with ethyl chloroformate, as well as with phosgene under the same experimental conditions failed to give the expected [1,4]benzoxazine derivatives. Unsuccessful were also our efforts for the synthesis of the corresponding fused ring systems of compounds **9**, **11** with 1,2,4,3,5-oxathiadiazol-2(3*H*)-one ring, *via* the reaction of **9**, **11** with thionylchloride.

The analytical and spectral data of new compounds resemble well with the structures suggested for them (see Experimental).

EXPERIMENTAL

Melting points are uncorrected and were measured on a Kofler hot-stage apparatus. IR spectra were obtained with a

Perkin-Elmer 1310 spectrophotometer as nujol mulls. Nmr spectra were recorded on a Bruker AM 300 (300 MHz, and 75 MHz), for ^1H and ^{13}C respectively, using deuteriochloroform as solvent and tetramethylsilane as an internal standard; *J* values are reported in Hz. Mass spectra were determined on a VG-250 spectrometer at 70 eV under Electron Impact (EI) conditions. High resolution mass spectra (hrms) were recorded on an Bruker Daltonics ICR-MS-APEX II mass spectrometer under Electrospray Ionization (ESI) conditions. MicroAnalyses were performed on a Perkin-Elmer 2400-II Element Analyzer. Analyses indicated by the symbols of the elements were within $\pm 0.4\%$ of the theoretical values. Silica gel N $^\circ$ 60, Merck A.G. has been used for column chromatographies.

Di[1,2,4]oxadiazolo[4,3-*a*:3,4-*c*]quinoxaline-3,10-dione (**2**).

A 20% solution of phosgene in toluene (1.5 ml, 0.297 g, 3 mmoles) was added dropwise during an hour, through a dropping funnel, to a solution of compound **1** (0.192 g, 1 mmole) and dry triethylamine (0.8 ml) in dry dioxane (20 ml) at rt, under stirring. The reaction mixture was stirred for 24 h. The precipitated triethylamine hydrochloride was removed by filtration, the solvent was evaporated in a rotary evaporator and the residue was subjected to a column chromatography (silica gel, hexane/ethyl acetate 6:1 up to 0:1) to give brown crystals of compound **2** (80 mg, 33%), m.p. 246-248°C (from ether); ir: 3060, 1810, 1790, 1640, 1585 cm^{-1} ; ^1H -nmr: δ 7.55-7.62 (m, 1H), 8.61-8.70 (m, 1H); ^{13}C -nmr: δ 116.1, 128.6, 148.1, 154.3, 162.9; ms (EI): *m/z* 244 (M^+ , 92%), 200 (78), 170 (48), 156 (72), 143 (52), 128 (32), 120 (56), 104 (100).

Anal. Calcd for $\text{C}_{10}\text{H}_4\text{N}_4\text{O}_4$: C, 49.12; H, 1.77; N, 22.93. Found: C, 48.84; H, 1.98; N, 23.20.

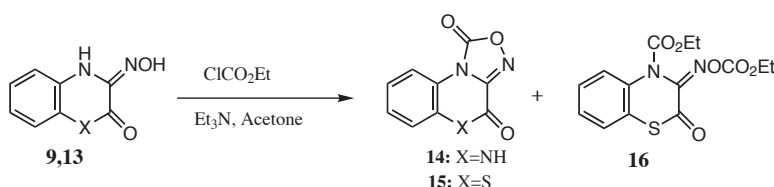
4,4a,8a,9-Tetrahydro[1,2,5]oxadiazolo[3,4-*b*]quinoxaline (**3**).

This compound was obtained from the above described reaction between **1** and phosgene and eluted after compound **2** (32 mg, 18%), m.p. 244-246°C (lit. [13] m.p. 244-246°C).

Di[1,2,4]oxadiazolo[4,3-*a*:3,4-*c*]quinoxaline-3,10-dithione (**4**).

A solution of thiophosgene (0.206 g, 1.79 mmoles) in benzene (1.65 ml) was added dropwise during an 1.5 h period to a solution of compound **1** (0.172 g, 0.89 mmole) and dry triethylamine (0.5 ml) in dioxane (20 ml) under stirring at rt. The reaction mixture was stirred for further 16 h. The precipitated triethylamine hydrochloride was filtered, the solvent was removed in a rotary evaporator and the residue was chromatographed (silica gel, hexane/ethyl acetate 9:1) to give light yellow crystals of compound **4** (75 mg, 31%), m.p. 223-225°C (d); ir: 3040, 1605, 1580 cm^{-1} ; ^1H -nmr: δ 7.58-7.63 (m); ^{13}C -nmr: δ 116.3, 117.1, 152.1, 156.6, 161.3; ms (EI): *m/z* 276 (M^+ , 100%), 216 (8), 188 (90), 156 (8), 136 (16), 104 (62).

Scheme 4



Anal. Calcd for $C_{10}H_4N_4O_2S_2$: C, 43.44; H, 1.56; N, 20.28. Found: C, 43.78; H, 1.70; N, 20.30.

Compound **3** (28 mg, 18%) was eluted next.

$1\lambda^4, 6\lambda^4$ -Di[1,2,3,5]oxathiadiazolo[3,4-*a*:4,3-*c'*]quinoxaline-1,6-dione (**5**).

A solution of thionylchloride (0.264 g, 2.21 mmol) in dry THF (15 ml) was added dropwise during 3 h at rt under stirring to a solution of compound **1** (0.192 g, 1 mmol) and dry pyridine (0.312 g, 3.95 mmol) in dry THF (20 ml). The reaction mixture was stirred for further 24 h and then was filtered. The solvent was evaporated in a rotary evaporator and the residue was subjected to column chromatography to give orange crystals of compound **5** (96 mg, 34%), m.p. 186–188°C (d); ir: 3060, 1635, 1605, 1500 cm^{-1} ; 1H -nmr: δ 7.74–7.85 (m, 1H), 7.95–8.04 (m, 1H); ^{13}C -nmr(CDCl₃-DMSO-*d*₆): δ 116.6, 130.8, 135.0, 156.1; ms (EI): *m/z* 284 (*M*⁺, 100%), 258 (6), 232 (50), 174 (14), 173 (92), 172 (74), 143 (80), 142 (83), 115 (25).

Anal. Calcd for $C_8H_4N_4O_4S_2$: C, 33.77; H, 1.52; N, 19.71. Found: C, 33.87; H, 1.53; N, 19.83.

1,4-Dihydro-2,3-quinoxalinedione 2-oxime (**9**).

A solution of triethylamine (1.335 g, 13.2 mmol) in chloroform (20 ml) was added to a solution of imidochloride **7** (2 g, 13.2 mmol) and *o*-phenylenediamine **8** (1.427 g, 13.2 mmol) in chloroform (120 ml) dropwise during 30 min under stirring at rt. After storage at room temperature, the precipitate was collected by filtration and washed with water to give yellow crystals of compound **9** (1.74 g, 87%), m.p. >300°C (from methanol/THF); ir: 3380, 3125, 3070, 1680, 1640, 1600, 1520 cm^{-1} ; 1H -nmr (CDCl₃-DMSO-*d*₆): δ 6.81 (t, *J*=7.3, 1H), 6.90 (t, *J*=7.3, 1H), 6.94 (d, *J*=7.3 Hz, 1H), 7.26 (d, *J*=7.3, 1H), 9.87 (s, 1H), 10.75 (s, 1H), 11.18 (s, 1H); ^{13}C -nmr(CDCl₃-DMSO-*d*₆): δ 113.9, 114.7, 120.2, 122.7, 124.3, 126.8, 140.1, 154.4; ms (EI): *m/z* 177 (*M*⁺, 53%), 161 (100), 147 (59), 133 (52), 119 (47), 105 (56), 104 (37), 90 (32).

Anal. Calcd for $C_8H_7N_3O_2$: C, 54.22; H, 3.98; N, 23.73. Found: C, 54.16; H, 4.27; N, 23.58.

2*H*-[1,4]Benzoxazine-2,3(4*H*)-dione 3-oxime (**11**).

To a solution of compound **7** (2 g, 13.2 mmol) and *o*-aminophenol **10** (1.44 g, 13.2 mmol) in dry ether (110 ml) a solution of dry triethylamine (1.335 g, 13.2 mmol) in ether (20 ml) was added dropwise, during 30 min, at rt, under stirring. After storage at rt the precipitate was collected by filtration and was washed with water to give light brown crystals of compound **11** (1.66 g, 83%), m.p. 288–290°C (d) (ether/methanol); ir: 3330, 3160, 3050, 1740, 1620, 1585, 1490 cm^{-1} ; 1H -nmr (CDCl₃-DMSO-*d*₆): δ 6.89 (t, *J*=6.9, 1H), 7.0–7.1 (m, 2H), 7.29 (d, *J*=6.9, 1H), 10.02 (s, 1H, exchanged by D₂O), 11.39 (s, 1H, exchanged by D₂O); ^{13}C -nmr(CDCl₃-DMSO-*d*₆): δ 114.5, 115.6, 120.4, 124.6, 125.6, 136.3, 138.7, 153.2; ms (EI): *m/z* 178 (*M*⁺, 42%), 161 (67), 147 (14), 134 (100), 119 (15), 105 (96), 104 (99), 91 (30).

Anal. Calcd for $C_8H_6N_2O_3$: C, 53.79; H, 3.62; N, 15.69. Found: C, 54.05; H, 3.49; N, 15.76.

2*H*-[1,4]Benzothiazine-2,3(4*H*)-dione 3-oxime (**13**).

To a solution of compound **7** (1 g, 6.5 mmol) and 2-aminothiophenol **12** (0.826 g, 6.5 mmol) in dry ether (50 ml) a solution of triethylamine (0.667 g, 6.5 mmol) in ether (10

ml) was added dropwise, during 20 min, at rt under stirring. After storage at rt the precipitate was collected by filtration and washed with water to give white crystals of compound **13** (0.84 g, 84%), m.p. 264–266°C (d); ir: 3230, 3150, 3030, 1680, 1625, 1580 cm^{-1} ; 1H -nmr (CDCl₃-DMSO-*d*₆): δ 7.02 (t, *J*=8.2, 1H), 7.11–7.21 (m, 2H), 7.26 (d, *J*=8.2, 1H), 10.48 (s, 1H), 12.92 (s, 1H); ^{13}C -nmr(CDCl₃-DMSO-*d*₆): δ 114.7, 117.0, 122.6, 125.1, 126.3, 132.8, 139.1, 152.9; ms (EI): *m/z* 194 (*M*⁺, 50%), 177 (17), 165 (56), 164 (56), 151 (83), 150 (42), 136 (88), 124 (100), 109 (99).

Anal. Calcd for $C_8H_6N_2O_2S$: C, 49.37; H, 3.33; N, 14.40. Found: C, 49.65; H, 3.58; N, 14.16.

[1,2,4]Oxadiazolo[4,3-*a*]quinoxaline-1,4(5*H*)-dione (**14**).

Ethyl chloroformate (0.216 g, 2 mmol) was added dropwise to a mixture of compound **9** (0.117 g, 1 mmol) and triethylamine (0.1 ml) in acetone (2.5 ml), at rt under stirring. The reaction mixture was left under stirring for further 12 h. The precipitated triethylamine hydrochloride was filtered off and the filtrate was concentrated in a rotary evaporator. The oily residue was treated with dichloromethane to give brown crystals of compound **14** (0.124 g, 70%), m.p. 268–270°C (d); ir: 3370, 3090, 1775, 1660, 1605, 1500 cm^{-1} ; 1H -nmr (CDCl₃-DMSO-*d*₆): δ 7.24–7.41 (m, 3H), 8.39 (d, *J*=7.9, 1H), 12.25 (s, 1H, exchanged by D₂O); ^{13}C -nmr(CDCl₃-DMSO-*d*₆): δ 114.3, 116.5, 123.7, 126.9, 132.8, 132.9, 149.2, 156.5, 160.1; ms (EI): *m/z* 203 (*M*⁺, 34%), 160 (31), 159 (28), 132 (32), 131 (30), 105 (86), 90 (32), 44 (100).

Anal. Calcd. for $C_9H_5N_3O_3$: C, 53.19; H, 2.48; N, 20.69. Found: C, 53.07; H, 2.29; N, 20.84.

4*H*-[1,2,4]Oxadiazolo[3,4-*c'*][1,4]benzothiazine-1,4-dione **15** and Ethyl 3-[(ethoxycarbonyl)oxy]imino}-2-oxo-2*H*-1,4-benzothiazine-4-carboxylate **16**.

To a solution of compound **13** (0.194 g, 1.0 mmol) and triethylamine (0.1 ml) in acetone (2.5 ml) ethyl chloroformate (0.216 g, 2 mmol) was added dropwise, at r.t. under stirring. The reaction mixture was stirred at r.t. for further 12 h and the precipitated triethylamine hydrochloride was then filtered off. The filtrate was concentrated in a rotary evaporator and the oily residue was triturated with methylene chloride to give at first compound **15** (11 mg, 6%), m.p. 233–235°C (dec.); ir: 1767, 1672, 1585, 1515 cm^{-1} ; 1H -nmr (CDCl₃): δ 7.11–7.36 (m, 4H); ^{13}C -nmr(CDCl₃): δ 118.0, 120.4, 124.3, 125.4, 128.0, 131.8, 137.2, 151.6, 158.2; ms (EI): *m/z* 220 (*M*⁺, 14%), 176 (100), 150 (52), 148 (38), 121 (29), 90 (30).

Anal. Calcd for $C_9H_4N_2O_3S$: C, 49.03; H, 1.96; N, 12.71. Found: C, 48.74; H, 2.29; N, 12.44.

Compound **16** was crystallised next (314 mg, 93%), m.p. 101–103°C; ir: 1755, 1725, 1670, 1620, 1515 cm^{-1} ; 1H -nmr (CDCl₃): δ 1.40 (t, 3H, *J*=6.9 Hz), 1.41 (t, 3H, *J*=6.9 Hz), 4.38 (q, 4H, *J*=6.9 Hz), 7.35–7.45 (m, 3H), 7.61–7.68 (m, 1H); ^{13}C -nmr (CDCl₃): δ 14.0, 14.2, 65.7, 65.9, 122.9, 124.9, 128.0, 129.3, 131.6, 135.8, 143.7, 151.1, 174.8, 183.3. HRMS (ESI): *m/z* for [*M*+Na]⁺ $C_{14}H_{14}N_2NaO_6S$: 361.04666. Calcd: 361.04648.

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