Synthesis and Spectral Properties of Substituted [1,2,4]Oxadiazolo[4,5-*a*][1,5]benzodiazepines

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The preparation of twelve novel substituted [1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepines which have potentially useful pharmacological properties; by 1,3-dipolar cycloaddition of benzonitrile oxides, generated *in situ* from benzohydroxamoyl chloride and triethylamine, to 1,5-benzodiazepine derivatives, is described. The structure of all products was corroborated by ir, ^{1}H-nmr, ^{13}C-nmr and ms.

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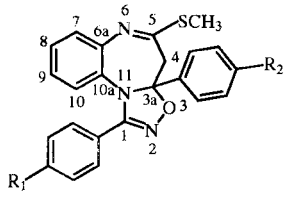
The synthesis of benzodiazepinic derivatives with heterocyclic rings annelated to the "*a*" [3-6], "*c*" [7] or "*d*" [8] sides of the heptatomic system has recently attracted interest of several research groups and consequently many reports and patents have appeared.

The fusion of a heterocyclic system to the benzodiazepine ring appears, in fact, specially promising for the synthesis of derivatives with a higher activity and specificity, provided that they show similar pharmacological profiles to the benzodiazepines from which they are derived. Recently research has been carried out on 3-*a*,4,5,6-tetrahydro[1,2,4]oxadiazolo[4,5-a][1,5] benzodiazepine derivatives [9] to confirm its pharmacological activity as an anticonvulsant drug [10]. As a part of a program directed towards the synthesis and spectral property determination of heterocyclic derivatives with possible pharmacological activity, we describe in this report a facile one-step synthesis of the novel compounds, substituted [1,2,4]oxadiazolo[4,5-a][1,5]benzodiazepines **III**, **1-12**, (Scheme 1) as shown in Scheme 2.

Scheme 1



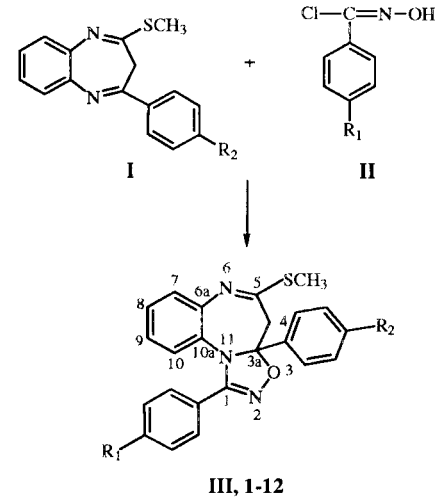
III, 1-12

	R_1	R_2
1	CH_3	CH_3
2	CH_3	OCH_3
3	CH_3	Cl
4	CH_3	Br
5	Cl	CH_3
6	Cl	OCH_3
7	Cl	Cl
8	Cl	Br
9	Br	CH_3
10	Br	OCH_3
11	Br	Cl
12	Br	Br

Our key intermediates **I** and **II** were prepared similarly to literature methods with modifications [11-13].

The reactions of Compounds **I** with a slight excess of benzonitrile oxide generated *in situ* from benzohydroxamoyl chloride **II**, and triethylamine, has been performed in chloroform under a nitrogen atmosphere at reflux for six hours. The oxadiazolo[4,5-*a*][1,5]benzodiazepines **III**, **1-12** have been obtained in 15-37% yield.

Scheme 2



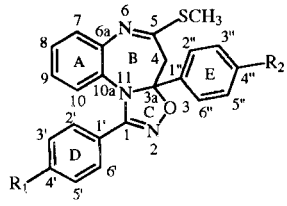
III, 1-12

The infrared spectrum of compounds **1-12** displayed absorptions at 1616-1586 cm^{-1} for C=H stretching; at 1228-1103 cm^{-1} for C-N stretching; at 1287-1098 cm^{-1} for C-O stretching and the corresponding absorptions for aromatic and R-substituents.

In the ^{1}H nmr spectra the presence of three proton signals at δ 2.24-2.50 singlet were assigned to the methyl protons joined to sulphur (S-CH_3). The presence of two proton signals at δ 2.91-2.97 and 3.19-3.24 singlet was consistent with the methylene protons of the C-4. The presence of four proton signals at δ 6.98-7.33 multiplet were assigned to the aromatic protons of the C-7; C-8; C-9 and C-10 of the benzodiazepine framework. The other aromatic protons appeared as a singlet and AA'BB' system at δ 6.90-7.58, and the signal for the R-substituent.

Table 1

^{13}C NMR Spectral Data For Compounds **1**,**2**,**5**,**7**,**9**, and **12**



III, [1,2,5,7,9,12]

Compounds	1	2	5	7	9	12
R_1	CH_3	CH_3	Cl	Cl	Br	Br
R_2	CH_3	OCH_3	CH_3	Cl	CH_3	Br
C-1	157.1	157.1	156.2	156.2	156.3	156.3
C-3a	112.2	112.3	112.8	111.7	112.8	111.8
C-4	44.5	44.5	44.6	44.2	44.6	44.2
C-5	171.2	171.1	171.4	170.8	171.4	170.8
C-6a	131.0	131.0	130.5	129.6	131.6	130.5
C-7	130.4	130.2	130.5	130.3	130.4	131.7
C-8	124.9	124.9	125.1	125.1	124.8	124.1
C-9	128.9	128.8	128.6	129.1	129.1	127.5
C-10	125.8	125.8	125.9	126.2	125.7	125.2
C-10a	147.9	147.9	148.2	147.7	148.3	147.7
C-1'	122.5	122.5	123.9	123.6	124.3	123.5
C-2', C-6'	127.7	127.7	128.2	128.7	126.0	126.2
C-3', C-5'	129.0	129.0	129.3	129.9	129.3	129.9
C-4'	140.5	140.5	136.4	136.6	141.2	139.4
C-1"	137.5	132.5	137.1	135.2	137.2	134.1
C-2", C-6"	128.9	127.3	129.1	129.3	129.2	129.3
C-3", C-5"	125.7	113.7	125.7	127.1	125.1	125.2
C-4"	138.9	160.1	139.3	138.8	139.1	138.3
$C = R_1$	21.1	21.4	-	-	-	-
$C = R_2$	21.4	55.3	21.1	-	21.2	-
S-CH_3	14.1	14.1	14.2	14.2	14.2	14.2

Note: The numbering of the phenyl ring is only for the assignment of the chemical shifts of the carbons in ^{13}C nmr Spectra.

The ^{13}C nmr spectra of compounds **1**, **2**, **5**, **7**, **9** and **12** are given in Table 1, and the signals were confirmed by using HETCOR, HETCOR Long Range, COSY, and NOESY nmr experiments operating at 500 MHz.

The mass spectra of the compounds **1-12** exhibit a stable molecular ion, the relative abundance of the principal fragment ions have some common features was confirmed by using ms/ms Tandem technics, and high resolution with accurate mass determination of the molecular ion and the principal fragments ions.

The main fragmentation pathways of **1-12** include ions at m/z $[104+R_2]^+$ the base peak; m/z $[M-47]^+$; m/z $[M-88]^+$; m/z $[281-R_2]^+$; m/z $[207+R_2]$, m/z $[102+R_1]^+$; m/z $[102+R_2]^+$, m/z $[76+R_2]^+$ m/z 218; 206; and 102, was consistent with the assigned structures.

EXPERIMENTAL

The ir spectra were recorded on a Nicolet Magna TR-750 spectrophotometer. The ^1H-nmr spectra were recorded on a Varian Unity-300 Spectrometer operating at 300 MHz and the ^{13}C-nmr spectra were recorded on a Varian Unity Plus-500. Spectrometer operating at 500 MHz, in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts δ (ppm) expressed downfield from TMS. The mass spectra were measured on a JEOL JMS-AX505 and JEOL MS-SX 102A High Resolution Mass Spectrometer with accurate mass determination of the molecular ion, using the direct inlet system. The spectra were recorded by electron impact at an ionization chamber temperature of 190° and ionizing electron energy of 70 eV.

General Procedure for the Synthesis of the 5-Methylthio-4*H*-1-(*p*-R_1-phenyl)-3a-(*p*-R_2-phenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepines, **III**, **1-12**.

To a stirred solution of the 4-(*p*-R_2-phenyl)-1,5-benzodiazepine derivatives I, (0.1 mole) in chloroform (5.0 ml), a solution of triethylamine (0.2 mole) in the same solvent (3.0 ml) was added dropwise over a few minutes; the mixture was kept under nitrogen atmosphere at reflux for 30-45 minutes. Subsequently was added dropwise a solution of benzohydroxamoyl chloride derivatives, **I**, (0.2 mole) in chloroform (5.0 ml) and the reaction mixture was stirred and heated at reflux for six hours, followed

by cooling to room temperature and the organic solution was dried (sodium sulfate) and evaporated in vacuo to yield a solid. The residual solid was purified on a silica gel chromatography column and elution with hexane-ethyl acetate (98:2) to yield the compounds **III**, **1-12** (15-37%).

5-Methylthio-4*H*-1-(*p*-methylphenyl)-3a-(*p*-methylphenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-a][1,5]benzodiazepine (**1**).

This compound was obtained as yellowish needles in 21% yield, mp 61°; ir (chloroform): ν C=N 1602, S-CH_3 1313, C-N 1110 and 1207, C-O 1058 and 1245 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.25 (s, 3H, S-CH_3), 2.35 (s, 3H, R_1 = CH_3), 2.49 (s, 3H, R_2 = CH_3), 2.96 (s, 1H, 4-H), 3.23 (s, 1H, 4-H), 6.98 (d, d, d, 1H, 8-H), 7.05 (d, d, 1H, 10-H), 7.14 (d, d, 1H, 7-H), 7.24 (d, d, d, 1H, 9-H), 7.02 and 7.54 (AA'BB', 4H, J = 8.0 Hz, phenyl protons of "E" ring), 7.20 and 7.28 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "D" ring); ms: m/z 413 (M^+), m/z 415 $[M+2]^+$.

Anal. Calcd. for $C_{25}H_{23}N_3OS$: C, 72.61; H, 5.60; N, 10.16. Found: C, 72.72; H, 5.68; N, 10.10.

5-Methylthio-4*H*-1-(*p*-methylphenyl)-3a-(*p*-methoxyphenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine (**2**).

This compound was obtained as yellowish needles in 18% yield, mp 44°; ir (chloroform): ν C=N 1595, S-CH_3 1318, C-N 1109 and 1212, C-O 1053 and 1254 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.28 (s, 3H, S-CH_3), 2.49 (s, 3H, R_1 = CH_3), 2.97 (s, 1H, 4-H), 3.23 (s, 1H, 4-H), 3.81 (s, 3H, R_2 = OCH_3), 7.01 (d, d, d, 1H, 8-H), 7.04 (d, d, 1H, 10-H), 7.13 (d, d, 1H, 7-H), 7.24 (d, d, d, 1H, 9-H), 6.90 and 7.58 (AA'BB', 4H, J = 8.0 Hz, phenyl protons of "E" ring), 7.02 and 7.28 (AA'BB', 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 429 (M^+), m/z 431 $[M+2]^+$.

Anal. Calcd. for $C_{25}H_{23}N_3O_2S$: C, 69.99; H, 5.40; N, 9.79. Found: C, 70.07; H, 5.33; N, 9.88.

5-Methylthio-4*H*-1-(*p*-methylphenyl)-3a-(*p*-chlorophenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-a][1,5]benzodiazepine (**3**).

This compound was obtained as yellowish needles in 16% yield, mp 45°; ir (chloroform): ν C=N 1605, S-CH_3 1322, C-N 1110 and 1212, C-O 1075 and 1286 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.24 (s, 3H, S-CH_3), 2.46 (s, 3H, R_1 = CH_3), 2.93 (s, 1H, 4-H), 3.19 (s, 1H, 4-H), 6.99 (d, d, d, 1H, 8-H), 7.10 (d, d, 1H, 10-H), 7.23 (d, d, 1H, 7-H), 7.27 (d, d, d, 1H, 9-H), 7.01 and 7.50 (AA'BB', 4H, J = 8 Hz, phenyl protons of "E" ring), 7.28 and 7.34 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "D" ring); ms: m/z 433 (M^+), m/z 435 $[M+2]^+$, m/z 437 $[M+4]^+$.

Anal. Calcd. for $C_{24}H_{20}ClN_3OS$: C, 66.43; H, 4.65; N, 9.69. Found: C, 66.53; H, 4.61; N, 9.61.

5-Methylthio-4*H*-1-(*p*-methylphenyl)-3a-(*p*-bromophenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine (**4**).

This compound was obtained as yellowish needles in 17% yield, mp 42°; ir (chloroform): ν C=N 1600, S-CH_3 1313, C-N 1103 and 1214, C-O 1070 and 1269 cm^{-1}; ^1H nmr (deuteriochloroform) δ 2.26 (s, 3H, S-CH_3), 2.48 (s, 3H, R_1 = CH_3), 2.93 (s, 1H, 4-H), 3.20 (s, 1H, 4-H), 7.05 (d, d, d, 1H, 8-H), 7.09 (d, d, 1H, 10-H), 7.22 (d, d, 1H, 7-H), 7.25 (d, d, d, 1H, 9-H), 7.52 (s, 4H, phenyl protons of "E" ring), 7.02 and 7.28 (AA'BB', 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 477 (M^+), m/z 479 $[M+2]^+$, m/z 481 $[M+4]^+$.

Anal. Calcd. for $C_{24}H_{20}BrN_3OS$: C, 60.25; H, 4.21; N, 8.79. Found: C, 60.10; H, 4.28; N, 8.73.

5-Methylthio-4*H*-1-(*p*-chlorophenyl)-3a-(*p*-methylphenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine (**5**).

This compound was obtained as whitish needles in 16% yield, mp 67°; ir (chloroform): ν C=N 1598, S-CH_3 1315, C-N 1110 and 1214, C-O 1094 and 1256 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36 (s, 3H, S-CH_3), 2.5 (s, 3H, R_2 = CH_3), 2.95 (s, 1H, 4-H), 3.24 (s, 1H, 4-H), 7.13 (d, d, d, 1H, 8-H), 7.18 (d, d, 1H, 10-H), 7.23 (d, d, 1H, 7-H), 7.28 (d, d, d, 1H, 9-H), 7.05 and 7.53 (AA'BB', 4H, J = 8.0 Hz, phenyl protons of "E" ring), 7.16 and 7.33 (AA'BB', 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 433 (M^+), m/z 435 $[M+2]^+$, m/z 437 $[M+4]^+$.

Anal. Calcd. for $C_{24}H_{20}ClN_3OS$: C, 66.43; H, 4.65; N, 9.69. Found: C, 66.31; H, 4.73; N, 9.58.

5-Methylthio-4*H*-1-(*p*-chlorophenyl)-3a-(*p*-methoxyphenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine (**6**).

This compound was obtained as yellowish needles in 21% yield, mp 65°; ir (chloroform): ν C=N 1616, S-CH_3 1318, C-N 1111 and 1215, C-O 1089 and 1255 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.5 (s, 3H, S-CH_3), 2.95 (s, 1H, 4-H), 3.23 (s, 1H, 4-H), 3.80 (s, 3H, R_2 = OCH_3), 7.11 (d, d, d, 1H, 8-H), 7.16 (d, d, 1H, 10-H), 7.23 (d, d, 1H, 7-H), 7.28 (d, d, d, 1H, 9-H), 6.92 and 7.57 (AA'BB', 4H, J = 8 Hz, phenyl protons of "E" ring), 7.05 and 7.19 (AA'BB, 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 449 (M+), m/z 451 $[M+2]^+$, m/z 453 $[M+4]^+$.

Anal. Calcd. for $C_{24}H_{20}ClN_3O_2S$: C, 64.07; H 4.48; N, 9.34. Found: C, 64.14; H, 4.55; N, 9.22

5-Methylthio-4*H*-1-(*p*-chlorophenyl-3a-(*p*-chlorophenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine (**7**).

This compound was obtained as whitish needles in 15% yield, mp 79°; ir (chloroform): ν C=N 1602, S-CH_3 1314, C-N 1105 and 1218, C-O 1095 and 1265 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.5 (s, 3H, S-CH_3), 2.93 (s, 1H, 4-H), 3.22 (s, 1H, 4-H), 7.04 (d, d, d, 1H, 8-H), 7.19 (d, d, 1H, 10-H), 7.24 (d, d, 1H, 7-H), 7.29 (d, d, d, 1H, 9-H), 7.07 and 7.58 (AA'BB', 4H, J = 8 Hz, phenyl protons of "E" ring), 7.21 and 7.33 (AA'BB', 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 453 (M^+), m/z 455 $[M+2]^+$, m/z 457 $[M+4]^+$, m/z 459 $[M+6]^+$.

Anal. Calcd. for $C_{23}H_{17}Cl_2N_3OS$: C, 60.80; H, 3.77; N, 9.25. Found: C, 60.89; H, 3.71; N, 9.39.

5-Methylthio-4*H*-1-(*p*-chlorophenyl)-3a-(*p*-bromophenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine (**8**).

This compound was obtained as yellowish needles in 26% yield, mp 137°; ir (chloroform): ν C=N 1590, S-CH_3 1313, C-N 1155 and 1228, C-O 1098 and 1287 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.5 (s, 3H, s-CH_3), 2.92 (s, 1H, 4-H), 3.22 (s, 1H, 4-H), 7.05 (d, d, d, 1H, 8-H), 7.19 (d, d, 1H, 10-H), 7.25 (d, d, 1H, 7-H), 7.3 (d, d, d, 1H, 9-H), 7.06 and 7.53 (AA'BB', 4H, J = 8Hz, phenyl protons of "E" ring), 7.24 and 7.33 (AA'BB', 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 497 (M^+), m/z 499 $[M+2]^+$, m/z 501 $[M+4]^+$, m/z 503 $[M+6]^+$.

Anal. Calcd. for $C_{23}H_{17}BrClN_3OS$: C, 55.38; H, 3.44; N 8.43. Found: C, 55.22; H, 3.49; N, 8.30.

5-Methylthio-4*H*-1-(*p*-Bromophenyl)-3a-(*p*-methylphenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-a][1,5]benzodiazepine (**9**).

This compound was obtained as yellowish needles in 37%

yield, mp 64°; ir (chloroform): ν C=N 1605, S-CH_3 1313, C-N 1153 and 1214, C-O 1072 and 1217 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36 (s, 3H, S-CH_3), 2.49 (s, 3H, R_2 = CH_3), 2.95 (s, 1H, 4-H), 3.24 (s, 1H, 4-H), 7.13 (d, d, d, 1H, 8-H), 7.18 (d, d, 1H, 10-H), 7.23 (d, d, 1H, 7-H), 7.32 (d, d, d, 1H, 9-H), 7.05 and 7.53 (AA'BB', 4H, J = 8 Hz, phenyl protons of "E" ring), 7.14 and 7.35 (AA'BB', 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 477 (M^+), m/z 479 $[M+2]^+$, m/z 481 $[M+4]^+$.

Anal. Calcd. for $C_{24}H_{20}BrN_3OS$: C, 60.25; H, 4.21; N, 8.79. Found: C, 60.33; H, 4.12; N, 8.87.

5-Methylthio-4*H*-1-(*p*-bromophenyl)-3a-(*p*-methoxyphenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine (**10**).

This compound was obtained as yellowish needles in 15% yield, mp 68°; ir (chloroform): ν C=N 1604; S-CH_3 1330; C-N 1156 and 1218; C-O 1074 and 1241 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H, S-CH_3), 2.95 (s, 1H, 4-H), 3.24 (s, 1H, 4-H), 3.82 (s, 3H, R_2 = OCH_3), 7.01 (d, d, d, 1H, 8-H), 7.13 (d, d, 1H, 10-H), 7.24 (d, d, 1H, 7-H), 7.27 (d, d, d, 1H, 9-H), 6.91 and 7.57 (AA'BB', 4H, J = 8 Hz, phenyl protons of "E" ring), 7.04 and 7.36 (AA'BB', 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 493 (M^+), m/z 495 $[M+2]^+$, m/z 497 $[M+4]^+$.

Anal. Calcd. for $C_{24}H_{20}BrN_3O_2S$: C, 58.30; H, 4.08; N, 8.50. Found: C, 58.36; H, 4.17; N, 8.39.

5-Methylthio-4*H*-1-(*p*-bromophenyl)-3a-(*p*-chlorophenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine (**11**).

This compound was obtained as yellowish needles in 18% yield, mp 66°; ir (chloroform): ν C=N 1602, S-CH_3 1330, C-N 1156 and 1218, C-O 1074 and 1241 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.47 (s, 3H, S-CH_3), 2.90 (s, 1H, 4-H), 3.19 (s, 1H, 4-H), 6.99 (d, d, d, 1H, 8-H), 7.21 (d, d, 1H, 10-H), 7.26 (d, d, 1H, 7-H), 7.33 (d, d, d, 1H, 9-H), 7.25 and 7.56 (AA'BB', 4H, J = 8 Hz, phenyl protons of "E" ring), 7.24 and 7.35 (AA'BB', 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 497 (M^+), m/z 499 $[M+2]^+$, m/z 501 $[M+4]^+$, m/z 503 $[M+6]^+$.

Anal. Calcd. for $C_{23}H_{17}Br\ ClN_3OS$: C, 55.38; H, 3.44; N, 8.43. Found: C, 55.49; H, 3.49; N, 8.31.

5-Methylthio-4*H*-1-(*p*-bromophenyl)-3a-(*p*-bromophenyl)-3a,4-dihydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine (**12**).

This compound was obtained as yellowish needles in 17% yield, mp 65°; ir (chloroform): ν C=N 1586, S-CH_3 1314, C-N 1125 and 1212, C-O 1073 and 1285 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.49 (s, 3H, S-CH_3), 2.91 (s, 1H, 4-H), 3.20 (s, 1H, 4-H), 7.04 (d, d, d, 1H, 8-H), 7.24 (d, d, 1H, 10-H), 7.30 (d, d, 1H, 7-H), 7.34 (d, d, d, 1H, 9-H), 7.52 (s, 4H, phenyl protons of "E" ring), 7.25 and 7.36 (AA'BB', 4H, J = 9 Hz, phenyl protons of "D" ring); ms: m/z 541 (M^+), m/z 543 $[M+2]^+$, m/z 545 $[M+4]^+$, m/z 547 $[M+6]^+$.

Anal. Calcd. for $C_{23}H_{17}Br_2N_3OS$: C, 50.84; H, 3.15; N, 7.74. Found: C, 50.98; H, 3.25; N, 7.60.

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[2] Contribution No. 1441 from instituto de Química, UNAM.

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