Salvador Vega,* María Esther Arranz [1] and Vicente J. Arán

Instituto de Química Médica, CSIC, Juan de la Cierva, 3, 28006 Madrid.
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Dedicated to Professor José Elguero on the occasion of his 70th birthday

Six bromomethyl derivatives of the new 2,3-dihydrooxazolo[3,2-*b*]thieno[3,4-*e*][1,2,4]thiadiazine 5,5-dioxides, 2,3-dihydrooxazolo[3,2-*b*]thieno[2,3-*e*][1,2,4]thiadiazine 5,5-dioxides and 6,7-dihydrooxazolo-[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-dioxides heterocyclic ring systems were synthesized. These compounds are good intermediates for the preparation and development of promising antiviral and psychotropic drugs. The structures of the products are supported by different nmr spectroscopic methods and mass spectrometry.

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Our interest in the potential biological activity of novel heterocyclic sulfonamides led us to synthesize an important number of derivatives of several new heterocyclic ring systems like, for example, S,S-dioxides of 1,2,4-benzothiadiazepine, thienoisothiazole, thieno- and pyrazolo[2,1]-benzothiazepine and thieno- and pyrazolo[1,2,4]-thiadiazine. Many of these derivatives showed excellent anti-inflammatory, psychotropic, cardiovascular and antiviral properties in the pharmacological tests [2-12].

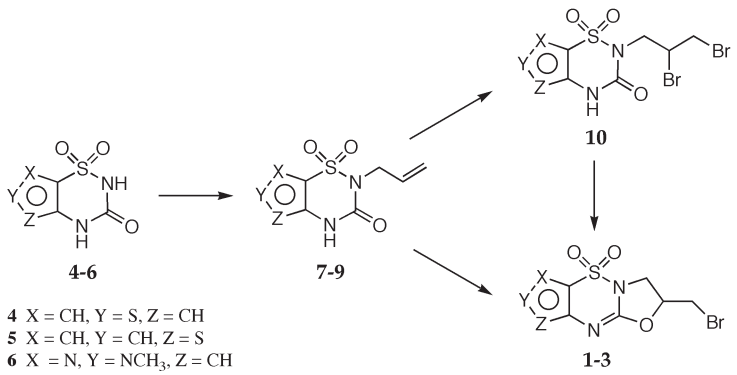
Within this research program, and looking for more active compounds, we planned to prepare three bromomethyl derivatives of dihydrooxazolo[3,2-*b*]hetero[1,2,4]thiadiazine S,S-dioxides **1-3** as key intermediates for the elaboration and development of promising antiviral and psychotropic drugs. The synthesis of these compounds and some closely related derivatives, which belong to the hitherto unknown oxazolo[3,2-*b*]thieno[3,4-*e*][1,2,4]thiadiazine 5,5-dioxides, oxazolo[3,2-*b*]-thieno[2,3-*e*][1,2,4]thiadiazine 5,5-dioxides and oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-dioxides heterocyclic ring systems, as well as the chemical and spectroscopic studies carried out for their characterization are the subject of the present report.

Our planned synthetic approach for the formation of compounds **1-3** is depicted in Scheme 1; it involves the alkylation of the previously described 1,2,4-thiadiazines **4-6** [13] with allyl bromide followed by cyclization of the thus formed 2-allyl derivatives **7-9** by reaction with bromine or N-bromosuccinimide.

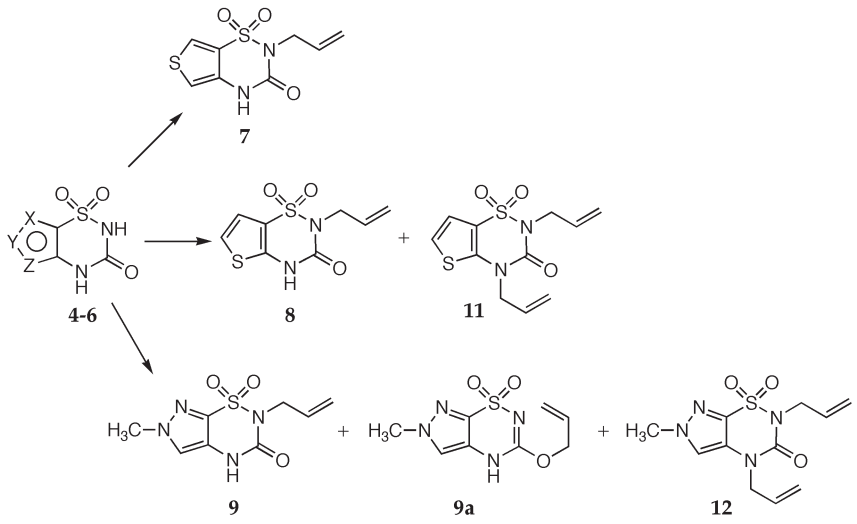
Alkylation of compounds **4-6** under classical conditions with allyl bromide in the presence of sodium hydride and *N*,*N*-dimethylformamide afforded the expected 2-allylheterothiadiazines **7-9** but with different results (Scheme 2). Thus, while the thieno[3,4-*e*]thiadiazine **4** gave in this reaction the N-2-allyl derivative **7** (61%) as the sole product, its thieno[2,3-*e*] isomer **5** furnished a mixture of the mono (N-2) and diallyl (N-2, N-4) compounds **8** and **11** in 68 and 7% yield, respectively. Under the same conditions, allylation of the pyrazole analogue **6** produced a mixture of compounds from which the N-2 and O-3 monoalkylated regioisomers **9** (42%) and **9a** (12%), as well as the N-2, N-4-diallyl derivative **12** (7%) were isolated.

The transformation of the 2-allylthiadiazines **7-9** into the target tricyclic compounds **1-3** was carried out through two known strategies. The first one, which had been successfully employed in the preparation of quinazolines [14], involves the addition of bromine to the allylic double bond of **7-9** and subsequent ring closure, in basic media, of the formed dibromo-intermediates. This strategy was long and

Scheme 1



Scheme 2

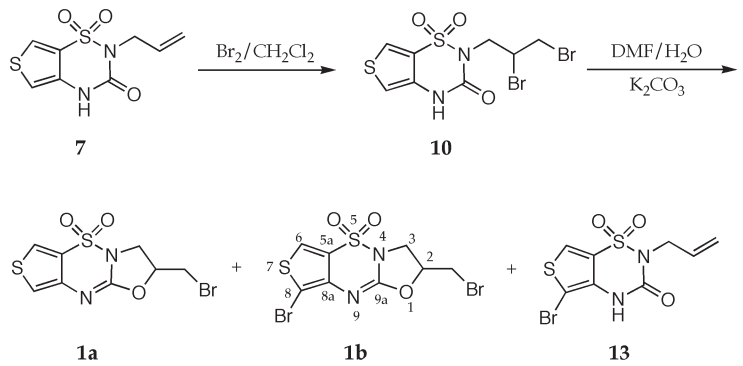


arduous and, therefore, it was only used in the transformation of the thieno[3,4-*e*]thiadiazine **7** (Scheme 3). Thus, addition of bromine upon a solution of compound **7** in dichloromethane afforded the dibromo-compound **10**. Subsequent reaction of this latter compound with potassium carbonate in *N*,*N*-dimethylformamide-water gave a mixture of compounds from which the expected tricyclic thiadiazine **1a** (50%) and the side products **1b** (14%) and **13** (4%) were isolated by flash chromatography. The analytical and spectral data of these side products allowed to characterize them as the 8-bromo-2-(bromomethyl)oxazolo[3,2-*b*]thieno[3,4-*e*][1,2,4]thiadiazine 5,5-dioxide **1b** and the 2-allyl-5-bromothieno[3,4-*e*][1,2,4]thiadiazinone 1,1-dioxide **13**.

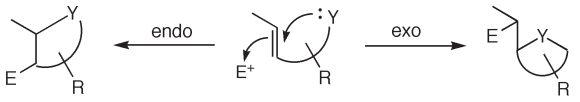
Although the structures of compounds **1a** and **1b** are very similar (both products exhibit in their ir spectra characteristic bands of the C=N bonds) it was possible to distinguish between them by examination of their proton nmr spectra. While the spectrum of **1a** clearly showed the typical two doublets of the two thiophene protons, these signals were not observed in the spectrum of **1b**, appearing instead of it a singlet at low field. Both compounds also showed a multiplet integrating for a proton which, due to its low field shift (ca. 5.30 ppm), was assigned to the C-2 proton of the oxazole ring. The structure of compound **13** was mainly determined by the absence in its ^{1}H nmr spectrum of the aforesaid thiophenic protons doublets and the presence in its ir spectrum of the typical stretching frequencies of NH and C=O groups at 3180 and 1680 cm^{-1}, respectively.

The second strategy, which was also applied to the synthesis of several heterocyclic ring systems [14-18], is based on the direct intramolecular halocyclization of compounds **7-9** with N-bromosuccinimide, facilitated by the relative proximity of the carbonyl and allyl groups of these molecules. It is known that this type of electrophylic cyclizations can take place with the formation of exo or endo derivatives (Scheme 4), and we reasoned that the bro-

Scheme 3

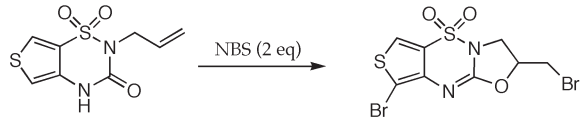


Scheme 4



mocyclization of compounds **7-9** with *N*-bromosuccinimide would follow Baldwin's rules [19] in which the exo ring closure would provide the target tricyclic 1,2,4-thiadiazines **1-3**. This strategy resulted more practical than the first one since the reaction is carried out in a one-pot process, without the troublesome use of bromine. Thus, reaction of the 2-allylthieno[3,4-*e*][1,2,4]thiadiazine **7** with two equivalents of *N*-bromosuccinimide in dichloromethane at room temperature (Scheme 5) yielded a single product (74%) whose physical and spectroscopic characteristics coincided with those of the dibromo compound **1b**, already obtained as a side product following the first strategy.

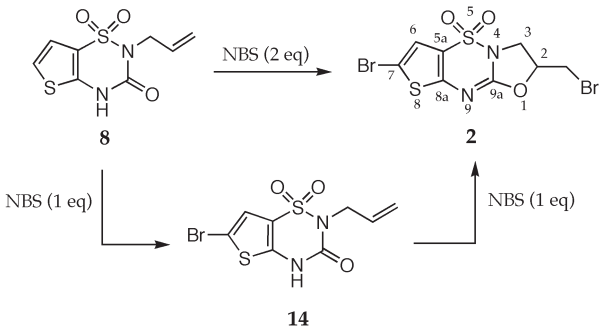
Scheme 5



7 **1b**

Under the same conditions the 2-allylthieno[2,3-*e*]-[1,2,4]thiadiazine **8** also led to a single product (89%) which was likewise identified as the dibromo compound **2** (Scheme 6). Attempts to avoid bromination in the thiophene ring of this heterocycle by changing the conditions of the original reaction (time, temperature, solvent) were not successful. However, when one equivalent of *N*-bromosuccinimide was used, the 2-allyl-6-bromothienothiadiazine **14** was formed in 80% yield, demonstrating the priority of the bromination process upon that of the ring closure. This latter process was carried out by reacting compound **14** again with *N*-bromosuccinimide giving the expected dibromo derivative **2**.

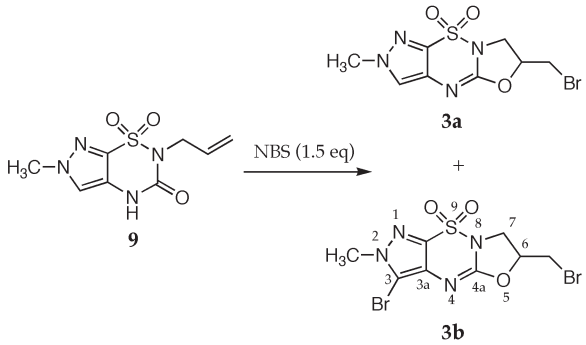
Scheme 6



8 **2** **14**

With respect to the 2-allylpyrazolo[4,3-*e*] analogue **9**, this reacted with *N*-bromosuccinimide in a similar way originating a mixture from which the required compound **3a** (58%) and the dihalogenated compound **3b** (26%) were isolated by flash chromatography (Scheme 7). These compounds were easily recognized by their ^{1}H nmr spectra. Although both compounds practically exhibited similar signals, only **3a** showed a singlet at 8.00 ppm, assigned to its pyrazole proton.

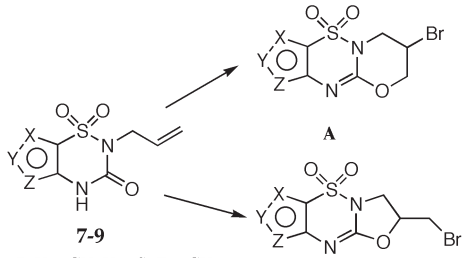
Scheme 7



9 **3a** **3b**

The differentiation between the structures **A** (endo) and **B** (exo) (Scheme 8), that theoretically could correspond to the compounds **1-3**, was firstly realized taking in account the information found in the bibliography [20-22] which postulated the structure **B** as the most probable for the final products. Nevertheless, this point was chemically confirmed by transformation of the 6-(bromomethyl) derivative **3a** in the compound **15** (Scheme 9) following a dehydrohalogenation reaction in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene. The study of the ^{13}C nmr spectro-

Scheme 8



7-9
7 X = CH, Y = S, Z = CH
8 X = CH, Y = CH, Z = S
9 X = N, Y = NCH$_3$, Z = CH

A **B**

Scheme 9

scopic data and DEPT (135º) experiments allowed to determine the exocyclic nature of the 6-C double bond of compound **15**. In fact, its ^{13}C nmr spectrum showed, in addition to the aromatic carbon chemical shifts, a signal at 42.9 ppm corresponding to a sp^3 carbon atom attached to two hydrogen atoms [NCH_2 (7-C)], a second signal at 88.7 ppm assigned to a sp^2 carbon atom also attached to two hydrogen atoms (H_2C=) and a quaternary carbon atom signal at 148.7 ppm (6-C). Logically, an endocyclic double bond would have shown in the ^{13}C nmr spectrum of **15** the signals corresponding to a methylene carbon atom (CH_2) and to two carbon atoms of CH= type. So that, it was concluded that the formation of an exocyclic double bond only can be explained with a structure of type **B** for compounds **1-3**.

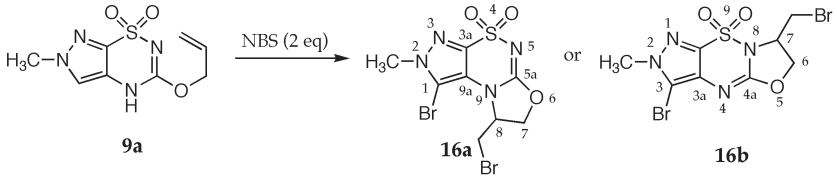
As expected, this second strategy was also successfully employed for the ring closure of the 3-(allyloxy)-pyrazolothiadiazine **9a** (Scheme 10). Treatment of this compound with *N*-bromosuccinimide under the above halocyclization conditions led to the formation of a single product **16** in 60% yield. The ^1H nmr data and elemental analysis of this latter product indicated that the ring closure of compound **9a** occurred with concomitant bromination of the pyrazole ring, but this information did not allow to determine on which of the two nitrogen atoms of thiadiazine ring the closure reaction took place.

As it is evident, the cyclization of **9a** could be accomplished on the N-4 position originating the angular tricyclic structure **16a** or on the N-2 position giving the linear system **16b**. The data obtained in the bibliography about the related 1,2,4-benzothiadiazines [23-26], in which also exists a tautomeric equilibrium, indicate that the C=N double bond is preferentially located between the 2- and 3-positions. Accordingly, the compound **9a** would be mainly in the 4H-tautomeric form, which would afford the angular tricyclic product **16a**. Nevertheless, in the coupled ^{13}C nmr spectrum of compound **16** we have not been able to detect the coupling of 9a-C with 8-H ($^3J_{C,H}$) which could only be expected in the angular structure **16a** and, consequently, there is not correlation between the mentioned C and H atoms in a HMBC experiment. Thus, we must conclude that compound **16** is best represented by the linear structure **16b**.

EXPERIMENTAL

Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. Ir spectra were recorded using a Shimadzu IR-435 instrument. ^1H nmr spectra (300 or 400 MHz) and ^{13}C nmr spectra (75 or 100 MHz) were measured with Varian XL-300 or Varian Inova 400 spectrometers in the indicated solvent. Chemical shift values are expressed in δ units relative to tetramethylsilane (TMS) as an internal standard. The assignments were made by means of different standard homo- and heteronuclear correlation experiments, mainly NOE, HMQC and HMBC. Mass spectra were recorded on a Hewlett-Packard 5973 MSD instrument. Silica gel/tlc cards (Fluka, silica gel-precoated aluminium cards with fluorescent indicator 254 nm) were used for thin-layer chromatography (tlc) which were run with cyclohexane-ethyl acetate mixtures (2:1 and 1:1 v/v) as eluents. Medium-pressure chromatography was performed on columns packed with silica gel 60 with (230-400 mesh) purchased from E. Merck, Inc. Elemental analysis were performed on a Heraeus CHN-RAPID instrument. Analytical results were found to be within ± 0.4% of the theoretical values.

Scheme 10



Synthesis of 2-Allylhetero[1,2,4]thiadiazinone 1,1-Dioxides and Related Compounds.

2-Allyl-2*H*-thieno[3,4-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxide (**7**).

To a solution of thieno[3,4-*e*][1,2,4]thiadiazinone 1,1-dioxide **4** (1.0 g, 4.9 mmol) in dry *N*,*N*-dimethylformamide (20 ml), under inert atmosphere, was added slowly sodium hydride (60% dispersion in mineral oil, 0.196 g, 4.9 mmol) and allyl bromide (0.42 ml,

4.9 mmol). The mixture was heated at 50° for 15 hours. After cooling, the reaction mixture was concentrated *in vacuo* and the crude residue was treated with water and extracted with dichloromethane. The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo*. The oily residue was purified by silica gel flash chromatography using hexane/ethyl acetate 2:1 and 1:1 v/v as eluents. Compound **7** (61%) was isolated as a crystalline solid of mp 106-108° (methanol-water); ir (potassium bromide): NH 3180, C=O 1692, SO_2 1335, 1170 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.35 (d, J = 5.6 Hz, 2H, 1'-H), 5.17 (d, J = 9.8 Hz, 1H, 3'-H_A), 5.21 (d, J = 15.8 Hz, 1H, 3'-H_B), 5.81-5.94 (m, 1H, 2'-H), 7.04 (d, J = 3.2 Hz, 1H, 5- or 7-H), 8.58 (d, J = 3.2 Hz, 1H, 7- or 5-H), 11.00 (broad s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 42.5 (1'-C), 106.9 (5-C), 117.7 (3'-C), 125.0 (7a-C), 126.2 (7-C), 132.3 (4a-C), 133.0 (2'-C), 149.0 (3-C); ms: m/z 245 (M^++1), 244.0 (M^+), 180.1 (M^+-SO_2), 97.2 ($C_4H_3NS^+$), 52.2 ($C_4H_4^+$).

Anal. Calcd. For $C_8H_8N_2O_3S_2$: C, 39.33; H, 3.30; N, 11.47; S, 26.25. Found: C, 39.24; H, 3.09; N, 11.23; S, 26.29.

2-Allyl-2*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**8**) and 2,4-Diallyl-2*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**11**).

These compounds were synthesized following the above procedure from the thieno[2,3-*e*][1,2,4]thiadiazinone 1,1-dioxide **5** (5.0 g, 24.5 mmol), *N*,*N*-dimethylformamide (100 ml), sodium hydride (60% dispersion in mineral oil, 0.98 g, 24.5 mmol) and allyl bromide (2.1 ml, 24.5 mmol). The mixture was heated at 50° for 72 hours. After silica gel flash chromatography of the residue, using hexane/ethyl acetate 2:1 and 1:1 v/v as eluents, compound **11** (0.52 g, 7.5%) was first isolated as a crystalline solid of mp 59-61° (ethanol-water); ir (nujol): C=O 1690, C=C 1645, SO_2 1320, 1175 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.41 (dt, J = 5.5 Hz, J = 1.4 Hz, 2H, 1'- or 1''-H), 4.58 (dt, J = 5.0 Hz, J = 1.7 Hz, 2H, 1''- or 1'-H), 5.15-5.29 (m, 4H, 3'- and 3''-H), 5.79-5.99 (m, 2H, 2'- and 2''-H), 7.41 (d, 2H, 6- and 7-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 43.3, 50.7 (1'- and 1''-C), 116.9 (7a-C), 118.0, 118.1 (3'- and 3''-C), 119.6, 119.9 (6- and 7-C), 130.6, 132.4 (2'- and 2''-C), 146.2 (4a-C), 148.4 (3-C); ms: m/z 284.0 (M^+), 200.9 ($C_7H_7NO_2S_2^+$), 137.1 ($C_7H_7NS^+$), 136.1 ($C_7H_6NS^+$), 41.2 ($C_3H_5^+$).

Anal. Calcd. For $C_{11}H_{12}N_2O_3S_2$: C, 46.46; H, 4.25; N, 9.85; S, 22.55. Found: C, 46.70; H, 4.18; N, 9.88; S, 22.80.

The slowest moving fractions gave compound **8** as a white solid (4.07 g, 68%) of mp 123-125° (ethanol-water): ir (potassium bromide): NH 3200, C=O 1680, SO_2 1320, 1140 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.35 (d, J = 5.5 Hz, 2H, 1'-H), 5.20 (dd, J = 10.2 Hz, J = 1.4 Hz, 1H, 3'-H_A), 5.22 (dd, J = 15.7 Hz, J = 1,4 Hz, 1H, 3'-H_B), 5.70-6.00 (m, 1H, 2'-H), 7.27 (d, 2H, 6- and 7-H), 12.07 (broad s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 42.0 (1'-C), 115.3 (7a-C), 118.0 (3'-C), 118.9 (6-C and 7-C), 132.7 (2'-C), 144.1 (4a-C), 148.5 (3-C); ms: m/z 244.0 (M^+), 97.2 ($C_4H_3NS^+$)), 52.3 ($C_4H_4^+$).

Anal. Calcd. For $C_8H_8N_2O_3S_2$: C, 39.33; H, 3.30; N, 11.47; S, 26.25. Found: C, 39.60; H, 3.08; N, 11.37; S, 26.01.

2-Allyl-6-methyl-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide (**9**), 3-(Allyloxy)-6-methyl-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazine 1,1-Dioxide (**9a**) and 2,4-Diallyl-6-methyl-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide (**12**).

These compounds were synthesized following the above procedure from the pyrazolo[4,3-*e*][1,2,4]thiadiazinone 1,1-dioxide **6** (1.0 g, 4.9 mmol), *N*,*N*-dimethylformamide (20 ml), sodium hydride (60% dispersion in mineral oil, 0.198 g, 4.9 mmol) and allyl bromide (0.42 ml, 4,9 mmol). The mixture was heated at 60° for 76 hours. Separation of the residue by silica gel flash chromatography, using chloroform/ethanol 9:1 v/v as eluent, yielded in the first fractions the diallyl derivative **12** (0.1 g, 7%) as an oil; ir (film): C=O 1687, SO_2 1330, 1150 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.89 (s, 3H, CH_3), 4.33 (d, J = 4.1 Hz, 2H, 1'- or 1''-H), 4.39 (d, J = 5.8 Hz, 2H, 1''- or 1'-H), 5.10-5.30 (m, 4H, 3'- and 3''-H), 5.60-6.00 (m, 2H, 2'- and 2''-H), 7.25 (s, 1H, 5-H); ms: m/z 281.9 (M^+), 134.0 ($C_7H_8N_3^+$), 42.1 ($C_3H_6^+$).

Anal. Calcd. For $C_{11}H_{14}N_4O_3S$: C, 46.80; H, 5.00; N, 19.84; S, 11.36. Found: C, 46.72; H, 5.02; N, 19.98; S, 11.25.

Compound **9** was isolated from the second fractions as a white crystalline solid (0.5 g, 42%) of mp 148-150° (ethanol); ir (potassium bromide): C=O 1703, SO_2 1342, 1175 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.95 (s, 3H, CH_3), 4.33 (d, J = 5.4, 2H, 1'-H), 5,15 (dd, J = 4.5 Hz, J = 1.4 Hz, 1H, 3'-H_A), 5.19 (dd, J = 11.5 Hz, J = 1.4 Hz, 1H, 3'-H_B), 5.72-5.96 (m, 1H, 2'-H), 7.75 (s, 1H, 5-H), 11.00 (broad s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 40.1 (CH_3), 41.8 (1'-C), 117.7 (3'-C), 118.4 (5-C), 120.5 (4a-C), 133.0 (2'- and 7a-C), 148.9 (3-C); ms: m/z 243.2 (M^++1), 242.2 (M^+), 96.3 ($C_4H_5N_2^+$), 56.3 ($C_3H_6N^+$), 42.3 ($C_3H_6^+$).

Anal. Calcd. For $C_8H_{10}N_4O_3S$: C, 39.66; H, 4.16; N, 23.13; S, 13.24. Found: C, 40.00; H, 3.98; N, 22.89; S, 13.50.

The slowest moving fractions gave the 3-allyloxithiadiazine **9a** as a white solid (0.14 g, 12%) of mp 68-70° (ethanol-water): ir (potassium bromide): NH 3240, SO_2 1325, 1150 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.94 (s, 3H, CH_3), 4.77 (d, J = 5.6 Hz, 2H, 1'-H), 5.29 (dd, J = 10.4 Hz, J = 1.3 Hz, 1H, 3'-H_A), 5.41 (dd, J = 17.2 Hz, J = 1,3 Hz, 1H, 3'-H_B), 5.80-6.20 (m, 1H, 2'-H), 7.79 (s, 1H, 5-H), 11.90 (broad s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 40.3 (CH_3), 68.7 (1'-C), 118.1 (5-C), 119.1 (3'-C), 121.4 (4a-C), 131.8 (2'-C), 134.0 (7a-C), 151.5 (3-C); ms: m/z 243.2 (M^++1), 242.2 (M^+), 96.4 ($C_4H_5N_2^+$), 56.3 ($C_3H_6N^+$), 42.3 ($C_3H_6^+$).

Anal. Calcd. For $C_8H_{10}N_4O_3S$: C, 39.66; H, 4.16; N, 23.13; S, 13.24. Found: C, 39.92; H, 4.37; N, 22.98; S, 13.53.

Synthesis of 2-Allyl-6-bromo-2*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**14**).

To a solution of 2-allylthieno[2,3-*e*][1,2,4]thiadiazinone 1,1-dioxide **8** (0.5 g, 2.0 mmol) in dry tetrahydrofuran (15 ml), *N*-bromosuccinimide (0.36 g, 2.0 mmol) was added. The mixture was maintained at room temperature for 30 hours. The solvent was evaporated to dryness *in vacuo* and the crystalline residue was washed with water and recrystallized from ethanol to give a white solid (80%) of mp 152-154°; ir (potassium bromide): C=O 1667, SO_2 1340, 1170 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.34 (d, J = 5.4 Hz, 2H, 1'-H), 5.16 (dd, J = 6.8 Hz, J = 1.4 Hz, 1H, 3'-H_A), 5.23 (dd, J = 13.8 Hz, J = 1.4 Hz, 1H, 3'-H_B), 5.70-6.00 (m, 1H, 2'-H), 7.63 (s, 1H, 7-H), 12.00 (broad s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 42.2 (1'-C), 104.1 (6-C), 115.4 (7a-C), 118.1 (3'-C), 121.7 (7-C), 132.5 (2'-C), 144.2 (4a-C), 148.1 (3-C); ms: m/z 324.0 (M^++2), 321.9 (M^+), 240.9 ($C_4H_2BrNO_2S_2^+$), 177.0 ($C_4H_2BrNS^+$), 96.0 ($C_4H_2NS^+$), 52.1 ($C_4H_4^+$).

Anal. Calcd. For $C_8H_7BrN_2O_3S_2$: C, 29.73; H, 2.18; N, 8.67; S, 19.84. Found: C, 29.52; H, 2.41; N, 8.55; S, 20.05.

Synthesis of Bromomethyl Derivatives of Oxazolo[3,2-*b*]hetero[1,2,4]thiadiazine S,S-Dioxides.

Method A. Reaction with Bromine.

2-(2,3-Dibromopropyl)-2*H*-thieno[3,4-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**10**).

2-Allylthieno[3,4-*e*][1,2,4]thiadiazinone 1,1-dioxide **7** (1.0 g, 4.1 mmol) was dissolved in dry dichloromethane and the solution cooled to 0°. Then, bromine (0.22 ml, 4.2 mmol) was added dropwise during 1 hour. The reaction mixture was stirred for 2 h at 0° and then allowed to warm to room temperature and stirred for an additional 2 hours. Compound **10** precipitated as a white solid (1.25 g) which was collected by filtration and washed with cold methylene chloride. It was pure enough to be used as such in the following step.

2-(Bromomethyl)-2,3-dihydrooxazolo[3,2-*b*]thieno[3,4-*e*]-[1,2,4]thiadiazine 5,5-Dioxide (**1a**), 8-Bromo-2-(bromomethyl)-2,3-dihydrooxazolo[3,2-*b*]thieno[3,4-*e*][1,2,4]thiadiazine 5,5-Dioxide (**1b**) and 2-Allyl-5-bromo-2*H*-thieno[3,4-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**13**).

A mixture of dibromopropyl compound **10** (0.6 g, 1.5 mmol), potassium carbonate (0.2 g, 1.5 mmol), *N*,*N*-dimethylformamide (4 ml) and water (1 ml) was stirred for 12 hours at room temperature. Then, water (15 ml) was added and the precipitated solid was collected by filtration, washed with water and dried. The crude product was subjected to flash chromatography, using hexane/ethyl acetate 3:1 and 2:1 v/v as eluent. The 5-bromo derivative **13** (0.02 g, 4%) was first isolated as a white solid of mp 185-187°: ir (potassium bromide): NH 3180, C=O 1680, SO_2 1340, 1165 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.32 (d, J = 5.4 Hz, 2H, 1'-H), 5.15 (dd, J = 4.5 Hz, J = 1.4 Hz, 1H, 3'-H_A), 5.22 (dd, J = 11.5 Hz, J = 1.4 Hz, 1H, 3'-H_B), 5.70-5.95 (m, 1H, 2'-H), 8.64 (s, 1H, 7-H), 11.30 (broad s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 42.8 (1'-C), 92.9 (5-C), 117.8 (3'-C), 126.1 (7a-C), 126.3 (7-C), 131.5 (4a-C), 132.7 (2'-C), 148.9 (3-C); ms: m/z 323.9 (M^++2), 321.9 (M^+), 179.1 ($C_8H_7N_2OS^+$)), 52.2 ($C_4H_4^+$).

Anal. Calcd. For $C_8H_7BrN_2O_3S_2$: C, 29.73; H, 2.18; N, 8.67; S, 19.84. Found: C, 30.02; H, 1.98; N, 8.48; S, 19.58.

The second fractions yielded the 8-bromo tricyclic derivative **1b** (0.084 g, 14%) as a white solid of mp 156-158°: ir (potassium bromide): C=N 1645, SO_2 1325, 1175 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.80-4.10 (m, 3H, 3-H_A and CH_2Br), 4.30 (t, J = 8.8 Hz, 1H, 3-H_B), 5.33 (m, 1H, 2-H), 8.85 (s, 1H, 6-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 34.1 (CH_2Br), 43.7 (3-C), 76.4 (2-C), 102.9 (8-C), 124.3 (5a-C), 127.1 (6-C), 140.4 (8a-C), 154.4 (9a-C); ms: m/z 404.7 (M^++4), 403.7 (M^++3), 402.7 (M^++2), 401.7 (M^++1), 400.7 (M^+), 399.7 (M^+-1), 267.8 (M^+-C_3H_5BrN), 204.1 ($C_5HBrNOS^+$), 201.9 ($C_5HBrNOS^+$), 123.2 (C_5HNOS^+), 81.2 (C_4HS^+), 56.2 ($C_4H_8^+$).

Anal. Calcd. For $C_8H_6Br_2N_2O_3S_2$: C, 23.89; H, 1.50; N, 6.97; S, 15.95; Br, 39.75. Found: C, 24.02; H, 1.60; N, 6.86; S, 15.78; Br, 39.53.

The slowest moving fractions gave compound **1a** (0.24 g, 50%) as a white solid of mp 125-127° (ethanol); ir (potassium bromide): C=N 1642, SO_2 1330, 1185 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.89 (dd, J = 11.5 Hz, J = 4.5 Hz, 1H, CH_ABr), 3.91 (dd, J = 8.8 Hz, J = 6.1 Hz, 1H, 3-H_A), 3.98 (dd, J = 11.5 Hz, J = 3.8, 1H, CH_BBr), 4.28 (t, J = 8.8 Hz, J = 8.8 Hz, 1H, 3-H_B), 5.29 (m, 1H, 2-H), 7.44 (d, J = 3.2 Hz, 1H, 6- or 8-H), 8.73 (d, J = 3.2 Hz, 1H, 8- or 6-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 34.1 (CH_2Br), 43.5 (3-C), 75.8 (2-C), 116.3 (8-C), 124.2 (5a-C), 126.8 (6-C), 142.2 (8a-C), 153.5 (9a-C); ms: m/z 323.9 (M^++2), 321.9 (M^+), 188.1 ($C_5H_2NO_3S_2^+$), 124.3 ($C_5H_2NOS^+$), 82.2 ($C_4H_2S^+$), 45.3 ($C_2H_5O^+$).

Anal. Calcd. For $C_8H_7BrN_2O_3S_2$: C, 29.73; H, 2.18; N, 8.67; S, 19.84; Found: C, 30.00; H, 1.97; N, 8.62; S, 20.11.

Method B. Reaction with *N*-Bromosuccinimide.

General Procedure.

To a solution of the corresponding 2-allylhetero[1,2,4]thiadiazinone 1,1-dioxide (1 equivalent) in dry dichloromethane *N*-bromosuccinimide (1.5-2 equivalents) was added. The mixture was stirred at room temperature for 50-70 hours. Then, water was added and the organic layer was separated, dried (magnesium sulfate) and concentrated to dryness *in vacuo*. The residue was purified by silica gel flash chromatography.

8-Bromo-2-(bromomethyl)-2,3-dihydrooxazolo[3,2-*b*]thieno[3,4-*e*][1,2,4]thiadiazine 5,5-Dioxide (**1b**).

This compound was obtained from the 2-allylthieno[3,4-*e*][1,2,4]thiadiazinone 1,1-dioxide **7** after 50 hours of stirring. Silica gel flash chromatography of the residue (hexane-ethyl acetate 3:1 v/v as eluent) gave a white solid (74%) whose physical and spectroscopic characteristics were identical to those of the compound **1b** obtained by method A.

7-Bromo-2-(bromomethyl)-2,3-dihydrooxazolo[3,2-*b*]thieno[2,3-*e*][1,2,4]thiadiazine 5,5-Dioxide (**2**).

This compound was obtained from the 2-allylthieno[2,3-*e*][1,2,4]thiadiazinone 1,1-dioxide **8** after 50 hours of stirring. Silica gel flash chromatography of the residue (dichloromethane as eluent) gave compound **2** as a white solid (89%) of mp 134-136°; ir (potassium bromide): C=N 1623, SO_2 1345, 1180 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.93 (dd, J = 11.6 Hz, J = 4.4 Hz, 1H, CH_ABr), 3.99 (dd, J = 11.6 Hz, J = 3.6 Hz, 1H, CH_BBr), 4.02 (dd, J = 9.0 Hz, J = 6.2 Hz, 1H, 3-H_A), 4.39 (t, J = 9.0 Hz, 1H, 3-H_B), 5.38-5.43 (m, 1H, 2-H), 7.78 (s, 1H, 6-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 34.1 (CH_2Br), 44.2 (3-C), 77.0 (2-C), 106.1 (7-C), 115.7 (5a-C), 121.6 (6-C), 155.9, 157.4 (8a- and 9a-C); ms: m/z 401.8 (M^++2), 399.8 (M^+), 322.9 (M^++2-Br), 320.9 (M^+-Br), 265.8 ($C_5HBrNO_3S_2^+$), 267.9 ($C_5HBrNO_3S_2^+$), 176.0 (C_4HBrNS^+), 173.9 (C_4HBrNS^+), 56.1 ($C_3H_4O^+$).

Anal. Calcd. For $C_8H_6Br_2N_2O_3S_2$: C, 23.89; H, 1.50; N, 6.97; S, 15.95. Found: C, 23.85; H, 1.42; N, 7.06; S, 15.78.

6-(Bromomethyl)-2-methyl-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-Dioxide (**3a**) and 3-Bromo-6-(bromomethyl)-2-methyl-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-Dioxide (**3b**).

These compounds were obtained from the 2-allylpyrazolo[4,3-*e*][1,2,4]thiadiazinone 1,1-dioxide **9** after 60 hours of stirring. Silica gel flash chromatography of the residue (hexane/ethyl acetate 1:9 v/v as eluent) gave first compound **3b** as a white solid (26%) of mp 156-158°; ir (potassium bromide): C=N 1665, SO_2 1315, 1165 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.88-4.03 (m, 6H, CH_3, 7-H_A and CH_2Br), 4.32 (t, J = 8.9 Hz, 1H, 7-H_B), 5.34 (m, 1H, 6-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 34.3 (CH_2Br), 39.4 (CH_3), 43,6 (7-C), 76.3 (6-C), 108.3 (3-C), 129.7 (3a-C), 134.1 (9a-C), 153.9 (4a-C); ms: m/z 402.0 (M^++4), 400.0 (M^++2), 398.0 (M^+), 321.0 (M^+-Br), 319.1 (M^+-Br), 257.1 (M^+-$BrSO_2$), 255.1 (M^+-$BrSO_2$), 176.2 (M^+-Br_2SO_2), 56.1 ($C_3H_4O^+$).

Anal. Calcd. For $C_8H_8Br_2N_4O_3S$: C, 24.01; H, 2.01; N, 14.00; S, 8.01. Found: C, 24.33; H, 1.98; N, 13.97; S, 7.87.

The slowest moving fractions gave compound **3a** as a white solid (48%) of mp 129-131°; ir (potassium bromide): C=N 1655, SO_2 1330, 1185 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.84-4.00 (m, 6H, CH_3, 7-H_A and CH_2Br), 4.29 (t, J = 8.8 Hz, 1H, 7-H_B), 5.20 (m, 1H, 6-H), 8.00 (s, 1H, 3-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 34.3 (CH_2Br), 40.4 (CH_3), 43.4 (7-C), 75.8 (6-C), 124.7 (3-C), 130.5 (3a-C), 133.7 (9a-C), 153.3 (4a-C); ms: m/z 322.0 (M^++2), 320.0 (M^+), 186.0 ($C_5H_4N_3O_3S^+$), 42.3 ($C_3H_6^+$).

Anal. Calcd. For $C_8H_9BrN_4O_3S$: C, 29.92; H, 2.82; N, 17.45; S, 9.98. Found: C, 30.02; H, 2.92; N, 17,41; S, 9.81.

3-Bromo-7-(bromomethyl)-2-methyl-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-dioxide (**16b**).

This compound was obtained from the 3-(allyloxy)pyrazolo[4,3-*e*][1,2,4]thiadiazine 1,1-dioxide **9a** after 70 hours of stirring. Silica gel flash chromatography of the residue (chloroform/ethanol 15/1 v/v as eluent) gave compound **16b** as a white solid (60%) of mp 253-255°; ir (potassium bromide): C=N 1615, SO_2 1320, 1165 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.92-3.99 (m, 5H, CH_3 and CH_2Br), 4.65-4.68 (dd, J = 9.0 Hz, J = 2.4 Hz, 1H, 6-H_A), 4.87 (dd, J = 8.7 Hz, J = 9.0 Hz, 1H, 6-H_B), 5.35-5.38 (m, 1H, 7-H); ^{13}C nmr (dimethyl sulfoxide-d_6, coupled spectrum): δ 34.7 (m, ^1J = 155.6 Hz, ^2J = 12.8 Hz, ^3J = 6.3 Hz, CH_2Br), 39.2 (q, ^1J = 143.0 Hz, CH_3), 55.1 (m, ^1J = 154.5 Hz, ^2J = 1.9 Hz, ^2J =0.8 Hz, 7-C), 71.4 [m (structured t), ^1J = 160.2 Hz (and additional fine structure which could not be analyzed, J < 1 Hz), 6-C], 100.0 (q, ^3J = 3.1 Hz, 3-C), 118.1 (s, 3a-C), 134.5 (s, 9a-C), 154.5 (dd, ^3J = 5.1 Hz, ^3J = 3.2 Hz, 4a-C); ms: m/z 401.9 (M^++2), 399.8 (M^+), 397.8 (M^+-2), 307.0 (M^+-CH_2Br), 305.0 (M^+-CH_2Br), 201.0 ($C_5H_3BrN_3O^+$), 199.0 ($C_5H_3BrN_3O^+$), 119.9 ($C_5H_3N_3O^+$), 41.3 ($C_3H_5^+$).

Anal. Calcd. For $C_8H_8Br_2N_4O_3S$: C, 24.01; H, 2.01; N, 14.00; S, 8.01. Found: C, 24.31; H, 1.97; N, 13.98; S, 7.99.

Synthesis of 2-Methyl-6-methylene-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-Dioxide (**15**).

A solution of 6-(bromomethyl) derivative **3a** (0.1 g, 0.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.09 ml, 0.6 mmol) in dry toluene (8 ml) was refluxed, under inert atmosphere, for 4 hours. After cooling, water was added and the mixture was extracted with dichloromethane. The organic layer was separated, dried (magnesium sulfate) and concentrated to dryness *in vacuo*. The oily residue was subjected to silica gel flash chromatography, using dichloromethane/ethanol 30:1 v/v as eluent. Compound **15** (72%) was isolated as a crystalline solid of mp 230-232°; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.00 (s, 3H, CH_3), 4.68 (m, 1H, =CH_A), 4.87 (d, 2H, J = 2.3 Hz, 7-H), 4.97 (m, 1H, =CH_B), 8.11 (s, 1H, 3-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 40.4 (CH_3), 42.9 (7-C), 88.7 (=CH_2), 125.3 (3-C), 129.5 (3a-C), 134.1 (9a-C), 148.7 (6-C), 151.8 (4a-C).

Anal. Calcd. For $C_8H_8N_4O_3S$: C, 40.00; H, 3.36; N, 23.32; S, 13.35. Found: C, 39.82; H, 3.29; N, 23.41; S, 13.24.

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