Functionalized 5,6-Dihydro-2*H*-1,2,6-Thiadiazine 1,1-Dioxides. Synthesis, Structure and Chemistry

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Treatment of sulfamide **4a** and aryl-substituted sulfamides **4b-e** with ethyl 3,3-diethoxypropionate (**13**) provided a convenient procedure for the synthesis of functionalized 5,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides **14**. Key spectral properties of this novel class of heterocycles are reported. The generality and utility of this transformation is briefly explored.

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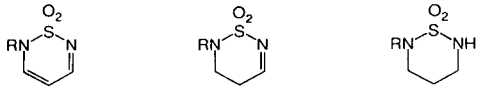
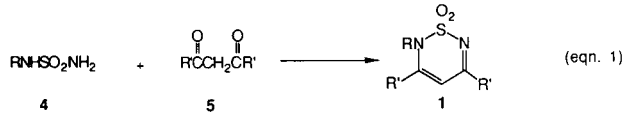
1,2,6-Thiadiazine 1,1-dioxide derivatives (*i.e.*, **1-3**) have found use in both synthesis and pharmacological studies [1,2]. Two general, *acid*-mediated procedures have been

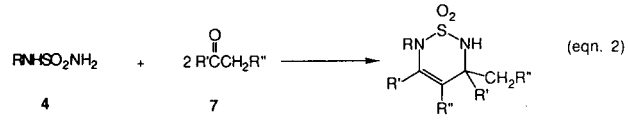


1 **2** **3**

reported for the preparation of this ring system [3]. The first entails the reaction of a sulfamide **4** with an equimolar amount of a 1,3-disubstituted compound **5** (*i.e.*, 1,3-dicarbonyl reagent, the corresponding acetal [1,2b,2d,-4], 1,3-diacid [2d], α,α-dicyano adduct [2a,c]) or an α,β-unsaturated carbonyl reagent [5] (equation 1). In this route one equivalent of each reactant is utilized for the construction of the thiadiazine 1,1-dioxide (*i.e.*, **1**). The second reaction requires the treatment of sulfamide **4** with two equivalents of a carbonyl compound [6] (*i.e.*, **7**) containing an acidic alpha hydrogen (equation 2). In this process, both equivalents of the carbonyl reagent are incorporated within the final heterocycle **8**. Recently, we have demonstrated that sulfamides **4** undergo α-sulfamidoalkylation



(eqn. 1)



(eqn. 2)

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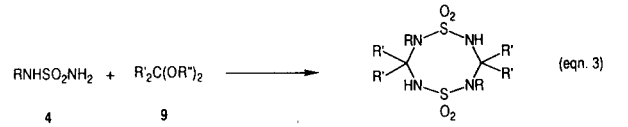
transformations upon treatment with acetals **9** in acid [7]. Both inter- (**10**) and intramolecular (**11, 12**) cyclized sulfamides (equations 3 and 4) were produced in moderate to high yields. In light of these multiple reaction pathways



(eqn. 3)

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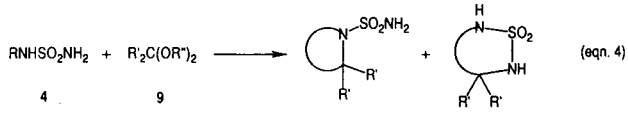
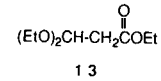


(eqn. 4)

11 **12**

we wished to determine whether treatment of sulfamides **4** with the masked 1,3-dicarbonyl reagent, ethyl 3,3-diethoxypropionate (**13**), in acid would generate the 1,2,6-thiadiazine 1,1-dioxide derivatives (*i.e.*, **1, 8**) or the α-sulfamidoalkylation products (*i.e.*, **10-12**).



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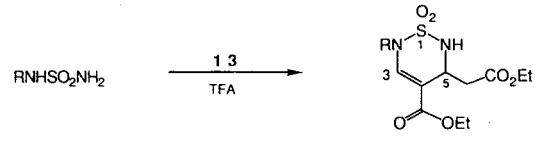
Results and Discussion.

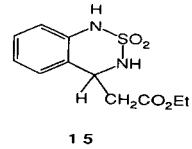
Treatment of sulfamide **4a** and the aryl-substituted sulfamides **4c-e** [8] with acetal **13** (2 equivalents) in trifluoroacetic acid gave as the major product (30-79% yield) the dihydro-1,2,6-thiadiazine 1,1-dioxide **14a, c-e**, respectively in which two equivalents of **13** were incorporated within the heterocycle [9]. Reduction of the molar ratio of **13** versus the sulfamide **4** led only to decreased yields of **14**. No significant changes in the product composition were detected under these conditions. Use of *N*-phenylsul-



4a R = H
b R = Ph
c R = CH_2Ph
d R = $(CH_2)_2Ph$
e R = $(CH_2)_3Ph$

14a R = H
b R = Ph
c R = CH_2Ph
d R = $(CH_2)_2Ph$
e R = $(CH_2)_3Ph$

famide (**4b**) in this protocol furnished both the dihydro-1,2,6-thiadiazine 1,1-dioxide **14b** (42%) and the intramolecular α-sulfamidoalkylation product **15** (41%).



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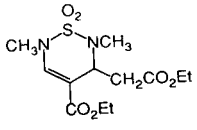
Compounds **14** were all thick oils and have been assigned as 5,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides on the basis of the observed ^1H and ^{13}C nmr spectral data. Distinctive signals were noted in the ^1H nmr spectra for the methine resonances at C-3 (δ 7.3-7.5) and C-5 (δ 4.5-4.8), and in the ^{13}C nmr spectra for the C-3 (140.7-141.9 ppm), the C-4 (100.2-106.1 ppm), and the two carboethoxy carbonyl (164.6-165.5, 170.1-171.4 ppm) peaks.

Significantly, in most previous syntheses of dihydro-1,2,6-thiadiazine 1,1-dioxides the corresponding tautomer **2** has been isolated in which the ring imine bond is located between C-3 and N-2 [6]. Preferential formation of the corresponding tautomer **14** in our study is believed to be due to the beneficial effects incurred by the placement of the endocyclic double bond in conjugation with the C(4)-carboethoxy group. Further support for the proposed assignment was secured by conversion of **14a** to the *N,N'*-dimethyl adduct **16** with excess methyl iodide and base. No significant changes were detected in the ^1H and ^{13}C nmr spectra of **16** versus **14a** upon *N*-alkylation.



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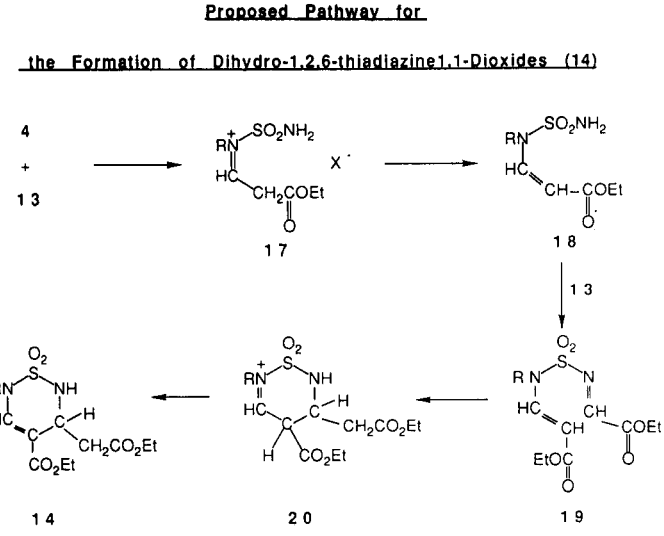
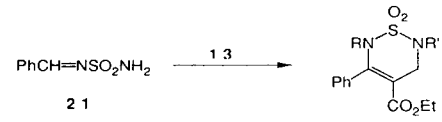
Formation of **14** is believed to proceed by the stepwise pathway depicted in Scheme 1. In agreement with this scenario, addition of **13** to *N*-benzylidenesulfamide (**21**)

Scheme 1



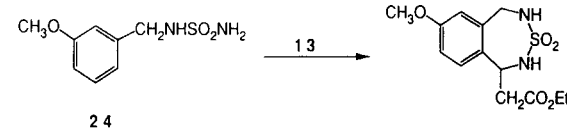
[10] in trifluoroacetic acid gave 4-carboethoxy-1,1-dioxo-5-phenyl-5,6-dihydro-2*H*-1,2,6-dithiadiazine (**22**) in 42% yield. Compound **22** was fully characterized as the *N,N'*-dimethyl derivative **23** after treatment with methyl iodide and base.



21

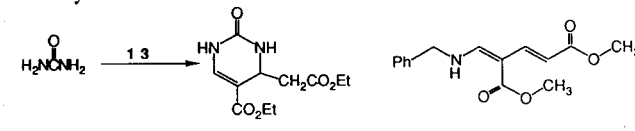
22 R,R'=H
23 R,R'=Me

Several preliminary experiments have been conducted which provide information concerning the generality and utility of this transformation. First, use of the electron-rich 3-methoxybenzylsulfamide (**24**) in place of benzylsulfamide (**4c**) gave the intramolecular α-sulfamidoalkylation product **25** rather than the corresponding dihydro-1,2,6-thiadiazine 1,1-dioxide **14** upon treatment with **13**. Second, substitution of urea for sulfamide (**4a**) in the ethyl



24 25

3,3-diethoxypropionate (**13**)-mediated reaction led to the production of the corresponding dihydropyrimidone derivative **26** [11]. Third, treatment of **16** with benzylamine in basic methanol furnished the novel acyclic adduct **27** in 63% yield.



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EXPERIMENTAL

General Methods.

Infrared spectra (ir) were run on a Perkin-Elmer 1130 spectrometer and calibrated against the 1601-cm^{-1} band of polystyrene. Absorption values are expressed in wavenumbers (cm^{-1}). Proton (^1H nmr) and carbon (^{13}C nmr) nuclear magnetic resonance spectra were taken on Nicolet NT-300 and General Electric QE-300 NMR instruments. Chemical shifts (δ) are in parts per million (ppm) relative to tetramethylsilane, and coupling constants (J values) are in hertz. Low-resolution electron-impact mass spectral data (MS) were obtained at an ionizing voltage of 70 eV on a Bell and Howell 21-491 mass spectrometer, and low-resolution FAB mass spectra were obtained on a Finnigan TSQ-70 spectrometer at the University of Texas-Austin under the auspices of Dr. David Laude. The high resolution FAB mass spectral data was obtained on a VG ZAB-SEQ instrument by Dr. Simon Gaskell and Mr. Ralph Orkiszewski at the Baylor College of Medicine. Microanalyses were obtained from Spang Microanalytical Laboratory, Eagle Harbor, MI.

All glassware was dried before use. The solvents and reactants were of the best commercial grade available and were used without further purification. Thin- and thick-layer chromatography were run on precoated silica gel GHLF microscope slides (2.5 x 10 cm, Analtech No. 21521) or silica gel GHLF (20 x 20 cm, Analtech No. 11187).

General Procedure for the Preparation of 5,6-Dihydro-2*H*-1,2,6-thiadiazine 1,1-Dioxides (**14**).

A trifluoroacetic acid (15 ml) solution containing sulfamide **4** (2 mmoles) and **13** (4 mmoles) was stirred at room temperature (2 days) and then concentrated to dryness *in vacuo*. The desired product was isolated by preparative tlc (chloroform).

Ethyl 4-Carbethoxy-1,1-dioxo-5,6-dihydro-2*H*-1,2,6-thiadiazin-5-ylacetate (**14a**).

Beginning with **4a** (0.19 g), **14a** was obtained in 38% yield (0.22 g), R_f 0.30 (30% acetone-chloroform); ir (chloroform): 3280, 3220, 1725, 1690, 1360, 1140 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.14-1.21 (m, 6H), 2.60 (dd, 1H, J = 15.8, 2.9 Hz), 2.98 (dd, 1H, J = 15.8, 11.2 Hz), 4.05-4.12 (m, 4H), 4.54-4.60 (m, 1H), 7.32 (s, 1H), 7.62 (d, 1H, J = 6.3 Hz, deuterium oxide exchangeable). The remaining N-H signal was not detected; ^{13}C nmr (dimethyl sulfoxide-d_6): 14.16, 14.33, 37.04, 59.26, 59.90, 61.64, 100.21, 141.93, 165.42, 170.55 ppm; ms: ($^-$FAB) 291 $[M-1]^-$; ms: ($^+$FAB) 293.08099 $[M+1]^+$ (calcd. for $C_{10}H_{17}N_2O_6S$, $[M+1]^+$, 293.08073), 239 (97), 276 (65), 265 (25), 247 (100), 214 (29), 205 (12), 197 (60), 168 (18), 116 (23).

Ethyl 4-Carbethoxy-2-benzyl-1,1-dioxo-5,6-dihydro-2*H*-1,2,6-thiadiazin-5-ylacetate (**14c**).

Beginning with **4c** (0.37 g), **14c** was obtained in 68% yield (0.52 g), R_f 0.38 (6% acetone-chloroform); ir (chloroform): 1730, 1670, 1620, 1380, 1170 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.08-1.30 (m, 6H), 2.69 (dd, 1H, J = 15.9, 2.8 Hz), 3.00 (dd, 1H, J = 15.9, 11.1 Hz), 4.06-4.19 (m, 4H), 4.61-4.66 (m, 1H), 4.75 (½ ABq, 1H, J = 15.9 Hz), 4.85 (½ ABq, 1H, J = 15.9 Hz), 7.18-7.45 (m, 6H), 8.38 (d, 1H, J = 6.6 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): 14.15 (2C), 36.69, 51.27, 51.66, 60.03, 60.19, 104.12, 127.80, 128.61, 136.37, 141.39, 164.61, 170.07 ppm; ms: m/e (relative intensity) 382 (6), 337 (14), 318 (100), 295 (52), 289 (10), 246 (12), 245 (26), 243 (24), 231 (33), 91 (56).

Anal. Calcd. for $C_{17}H_{22}N_2O_6S$: C, 53.39; H, 5.80; N, 7.33. Found: C, 53.70; H, 6.00; N, 7.18.

Ethyl 4-Carbethoxy-2-phenethyl-1,1-dioxo-5,6-dihydro-2*H*-1,2,6-thiadiazin-5-ylacetate (**14d**).

Beginning with **4d** (0.40 g), **14d** was obtained in 37% yield (0.29 g), R_f 0.35 (chloroform); ir (chloroform): 3400, 1730, 1705, 1350, 1130 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.23-1.30 (m, 6H), 2.77 (dd, 1H, J = 16.2, 3.2 Hz), 3.37 (dd, 1H, J = 16.2, 9.1 Hz), 3.05 (t, 2H, J = 7.4 Hz), 3.77-3.82 (m, 2H), 4.11-4.22 (m, 4H), 4.79-4.84 (m, 1H), 5.52 (d, 1H, J = 7.6 Hz, deuterium oxide exchangeable), 6.99 (s, 1H), 7.24-7.36 (m, 5H); ^{13}C nmr (deuteriochloroform): 14.09, 14.18, 36.05, 36.12, 51.64, 52.64, 60.40, 60.86, 104.21, 126.90, 128.68, 128.97, 137.16, 141.69, 164.81, 171.35 ppm; ms: m/e (relative intensity) 396 (1), 351 (2), 332 (17), 309 (11), 263 (11), 245 (9), 241 (16), 235 (13), 195 (13), 149 (13), 125 (15), 104 (100), 91 (35).

Anal. Calcd. for $C_{18}H_{24}N_2O_6S$: C, 54.53; H, 6.10; N, 7.07. Found: C, 54.63; H, 6.15; N, 6.98.

Ethyl 4-Carbethoxy-2-(3′-phenyl-*n*-propyl)-1,1-dioxo-5,6-dihydro-2*H*-1,2,6-thiadiazin-5-ylacetate (**14e**).

Beginning with **4e** (0.21 g), **14e** was obtained in 79% yield (0.65 g), R_f 0.45 (chloroform); ir (chloroform): 3340, 1715, 1680, 1350, 1160 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.15-1.24 (m, 6H), 1.90-1.97 (m, 2H), 2.61 (t, 2H, J = 7.7 Hz), 2.68 (dd, 1H, J = 16.0, 3.1 Hz), 2.99 (dd, 1H, J = 16.0, 11.1 Hz), 3.60 (t, 2H, J = 7.1 Hz), 4.07-4.18 (m, 4H), 4.58-4.65 (m, 1H), 7.17-7.74 (m, 5H), 7.46 (s, 1H), 8.27 (d, 1H, J = 6.7 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): 14.12, 14.24, 31.15, 31.75, 36.71, 49.15, 51.58, 59.94, 60.15, 103.56, 125.94, 128.24, 128.40, 141.07, 141.90, 164.75, 170.11 ppm; ms: m/e (relative intensity) 365 (1), 346 (16), 323 (27), 255 (96), 155 (27), 91 (100).

Anal. Calcd. for $C_{19}H_{26}N_2O_6S$: C, 55.59; H, 6.39; N, 6.83. Found: C, 55.65; H, 6.45; N, 6.70.

4-Carbethoxy-1,1-dioxo-5-phenyl-5,6-dihydro-2*H*-1,2,6-thiadiazine (**22**).

Beginning with **21** (0.37 g, 2 mmoles) and **13** (0.36 g, 2 mmoles), compound **22** was obtained in 42% yield (0.24 g), R_f 0.25 (chloroform); ir (chloroform): 3380, 3320, 1695 (br), 1350, 1150 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.04 (t, 3H, J = 7.0 Hz), 3.92-4.03 (m, 2H), 5.30 (d, 1H, J = 3.2 Hz), 7.19-7.42 (m, 6H), 7.54 (s, 1H), 7.70 (br s, 1H, deuterium oxide exchangeable); ^{13}C nmr (dimethyl sulfoxide-d_6): 14.17, 59.34, 57.41, 101.42, 127.14, 127.71, 127.93, 139.58, 140.74, 165.46 ppm; ms: ($^-$FAB) 281 $[M-1]^-$.

Preparation of 4-Carbethoxy-1,1-dioxo-2,6-dimethyl-5-phenyl-5,6-dihydro-2*H*-1,2,6-thiadiazine (**23**).

A mixture of **22** (0.28 g, 1 mmole), methyl iodide (0.58 g, 6 mmoles), potassium carbonate (1.38 g), and acetone (30 ml) was stirred at room temperature (30 hours). The solid was filtered and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by preparative tlc (chloroform) to give 0.26 g (86%) of **23** as a thick oil, R_f 0.57 (chloroform); ir (chloroform): 1690, 1335, 1120 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (t, 3H, J = 7.2 Hz), 2.92 (s, 3H), 3.26 (s, 3H), 4.13 (q, 2H, J = 7.2 Hz), 5.46 (s, 1H), 7.26-7.32 (m, 5H), 7.45 (s, 1H); ^{13}C nmr (deuteriochloroform): 14.07, 36.56, 60.49, 60.55, 66.20, 102.23, 127.60, 127.77, 127.89, 137.76, 141.90, 165.75 ppm.

Anal. Calcd. for $C_{14}H_{18}N_2O_4S$: C, 54.18; H, 5.85; N, 9.03. Found: C, 53.99; H, 5.89; N, 8.83.

Reaction of *N*-Phenylsulfamide (**4b**) with Ethyl 3,3-Diethoxypropionate (**13**).

The general procedure described for the preparation of **14** was employed using **4b** (0.17 g, 1 mmole), **13** (0.36 g, 2 mmoles) and trifluoroacetic acid (20 ml). Purification of the reaction mixture by preparative tlc (5% acetone-chloroform) afforded **14b** and **15**.

Ethyl 4-Carbethoxy-2-phenyl-1,1-dioxo-5,6-dihydro-2*H*-1,2,6-thiadiazin-5-ylacetate (**14b**).

This compound was obtained in 42% yield (0.11 g), R_f 0.35 (3% acetone-chloroform), mp 105-106°; ir (potassium bromide): 3270, 3200, 1720 (br), 1330, 1160 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.12-1.32 (m, 6H), 2.79 (dd, 1H, J = 16.0, 2.6 Hz), 3.09 (dd, 1H, J = 16.0, 11.1 Hz), 4.11-4.17 (m, 4H), 4.71-4.76 (m, 1H), 7.17-7.54 (m, 6H), 8.80 (d, 1H, J = 6.8 Hz); ^{13}C nmr (deuteriochloroform): 14.05, 14.19, 36.28, 52.68, 60.72, 60.99, 106.14, 126.17, 128.43, 129.59, 138.00, 141.44, 165.02, 171.39 ppm; ms: m/e (relative intensity) 368 (10), 304 (50), 281 (100), 275 (18), 257 (13), 253 (16), 231 (33), 212 (85), 189 (23), 171 (63).

Anal. Calcd. for $C_{16}H_{20}N_2O_6S$: C, 52.16; H, 5.47; N, 7.61. Found: C, 51.97; H, 5.76; N, 7.61.

Ethyl 2,2-Dioxo-3,4-dihydro-2,1,3-benzothiadiazin-4-ylacetate (**15**).

This compound was obtained in 41% yield (0.15 g), thick oil, R_f 0.30 (3% acetone-chloroform); ir (chloroform): 3440, 1720, 1690, 1370, 1180 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.22 (t, 3H, J = 7.0 Hz), 2.94-3.00 (m, 1H), 3.10-3.17 (m, 1H), 4.14 (t, 2H, J = 7.0 Hz), 4.85-4.95 (m, 1H), 6.73-6.76 (m, 1H), 6.92-6.97 (m, 1H), 7.18-7.24 (m, 2H), 7.49 (d, 1H, J = 7.0 Hz), 10.27 (s, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): 14.14, 38.83, 54.05, 60.28, 117.13, 121.72, 126.22, 128.35, 138.84, 170.38 ppm. The remaining aromatic signal was not detected and is presumed to be accidentally equivalent with one of the other observed signals; ms: m/e (relative intensity) 270 (27), 206 (42), 189 (22), 183 (100), 161 (85), 133 (42), 132 (46), 119 (81), 92 (54).

Anal. Calcd. for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.37. Found: C, 48.97; H, 5.23; N, 10.31.

Preparation of 4-Carbethoxy-2,6-dimethyl-1,1-dioxo-5,6-dihydro-2*H*-1,2,6-thiadiazin-5-ylacetate (**16**).

Compound **14a** (0.29 g, 1 mmole), methyl iodide (0.85 g, 6 mmoles) and potassium carbonate (1.38 g, 10 mmoles) were added to acetone (30 ml) and the mixture was stirred at room temperature (30 hours). The solid was filtered, and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by preparative tlc (chloroform) to give 0.27 g (85%) of **16**, mp 102-103°; ir (potassium bromide): 1750, 1710, 1340, 1140 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.26-1.32 (m, 6H), 2.80 (dd, 1H, J = 16.9, 3.4 Hz), 2.89 (s, 3H), 3.25 (s, 3H), 3.34 (dd, 1H, J = 16.9, 11.1 Hz), 4.15-4.23 (m, 4H), 4.68 (dd, 1H, J = 11.1, 3.4 Hz), 7.23 (s, 1H); ^{13}C nmr (deuteriochloroform): 14.13, 14.20, 36.40, 37.56, 40.41, 60.55, 61.01, 102.93, 141.43, 165.23, 171.62 ppm. The corresponding APT ^{13}C nmr spectrum indicated that the signal at 60.55 ppm consisted of two distinct resonances; ms: m/e (relative intensity) 320 (7), 275 (15), 233 (100), 226 (58), 205 (70), 180 (57), 169 (59), 152 (48).

Anal. Calcd. for $C_{12}H_{20}N_2O_6S$: C, 44.99; H, 6.29; N, 8.75. Found: C, 45.29; H, 6.39; N, 8.74.

Preparation of Ethyl 7-Methoxy-3,3-dioxo-1,2,4,5-tetrahydro-3,2,-4-thiadiazepin-1-ylacetate (**25**).

A solution of **24** (0.54 g, 2.5 mmoles), **13** (0.54 g, 2.5 mmoles) and trifluoroacetic acid (30 ml) was stirred at room temperature (5 days), and then concentrated to dryness *in vacuo*. The residue was recrystallized with ethanol to give 0.45 g (71%) of **25**, mp 231-232° dec; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.19 (t, 3H, J = 7.0 Hz), 2.85-2.93 (m, 1H), 2.99-3.07 (m, 1H), 3.75 (s, 3H), 4.00-4.15 (m, 3H), 4.26-4.35 (m, 1H), 4.75-4.80 (m, 1H), 6.82-6.93 (m, 4H), 7.13 (d, 1H, J = 8.5 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): 14.07, 38.55, 45.56, 50.67, 55.21, 60.10, 112.03, 116.00, 126.46, 132.45, 139.82, 158.33, 170.32 ppm; ms: m/e (relative intensity) 314 (3), 257 (12), 234 (27), 227 (100), 163 (36), 148 (55).

Anal. Calcd. for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.62; H, 5.82; N, 8.95.

Preparation of Ethyl 5-Carboethoxy-2-oxo-1,2,3,6-tetrahydro-1,3-diazin-4-ylacetate (**26**).

The general procedure described for the preparation of **14** was employed using urea (0.12 g, 2 mmoles) in place of **4a**. After preparative tlc (30% acetone-chloroform), **26** was obtained in 32% yield (0.16 g), R_f 0.29 (30% acetone-chloroform), mp 41-42°; ir (potassium bromide): 3210, 1720, 1695, 1660 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.07-1.29 (m, 6H), 2.47-2.50 (m, 2H), 3.97-4.10 (m, 4H), 4.43-4.47 (m, 1H), 7.14 (d, 1H, J = 5.1 Hz), 9.07 (br s, 1H), 9.70 (d, 1H, J = 5.1 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): 13.94, 14.20, 41.60, 48.09, 59.49, 60.02, 101.01, 137.40, 151.67, 164.60, 169.84 ppm; ms: m/e (relative intensity) 256 (24), 227 (13), 182 (73), 169 (100), 153 (14), 141 (78), 123 (28), 110 (35).

Anal. Calcd. for $C_{11}H_{16}N_2O_5$: C, 51.55; H, 6.29; N, 10.93. Found: C, 51.35; H, 6.45; N, 10.76.

Preparation of *N*-Benzylidenesulfamide (**21**).

A benzene (30 ml) solution containing benzaldehyde (2.12 g, 20 mmoles) and aniline (1.86 g, 20 mmoles) was heated to reflux (1 hour) using a Dean-Stark trap and then concentrated to dryness *in vacuo*. The residue was dissolved in an acetic acid (20 ml) solution containing **4a** (1.92 g, 20 mmoles) and acetic anhydride (2.24 g, 22 mmoles). The solution was heated at 100° (5 minutes) and then concentrated to dryness *in vacuo*. The residue was triturated with chloroform (20 ml). The solid which formed was filtered, washed with chloroform and dried to give 1.99 g (54%) of **21**, mp 131-133° (lit [10] mp 134°); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.45 (s, 2H), 7.57-7.73 (m, 3H), 8.00-8.02 (m, 2H), 8.95 (s, 1H).

Preparation of Methyl 5-(*N*-Benzylamino)-3-carbethoxy-2,4-pentadienoate (**27**).

To a sodium methoxide solution [prepared by addition of sodium (23 mg, 1 mmole) to methanol (30 ml)] was added **16** (0.32 g, 1 mmole) and benzylamine (0.13 g, 1.2 mmoles). The solution was heated at reflux (1 day) and then concentrated *in vacuo*. The residue was quenched with water (10 ml) and the mixture was extracted with ethyl ether (30 ml). The ethyl ether solution was washed with water, dried (sodium sulfate) and concentrated *in vacuo*. The residue was purified by preparative tlc (chloroform) to give 0.17 g (63%) of **27**, R_f 0.60 (10% acetone-chloroform), mp 106-107°; ir (potassium bromide): 3290, 1705, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.69 (s, 3H), 3.74 (s, 3H), 4.40 (d, 2H, J = 4.9 Hz), 6.03 (d, 1H, J = 15.6 Hz), 7.20-7.38 (m, 7H), 9.14-9.18 (m, 1H); ^{13}C nmr (deuteriochloroform): 50.73, 50.87, 52.80, 95.20, 108.02, 127.17, 128.00, 128.87, 136.68, 143.03, 156.74, 168.94, 169.94 ppm; ms: m/e (relative intensity) 275 (26), 243 (20), 201 (3), 156 (4), 91 (100).

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.23; N, 5.14. Found: C, 65.55; H, 6.32; N, 5.06.

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