Synthesis of Isomeric *N*-Substituted 5-Methyl-2*H*-1,2,6-Thiadiazin-3(6*H*)one 1,1-Dioxides from Sulfamides and Diketene (1)

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Received May 21, 1973

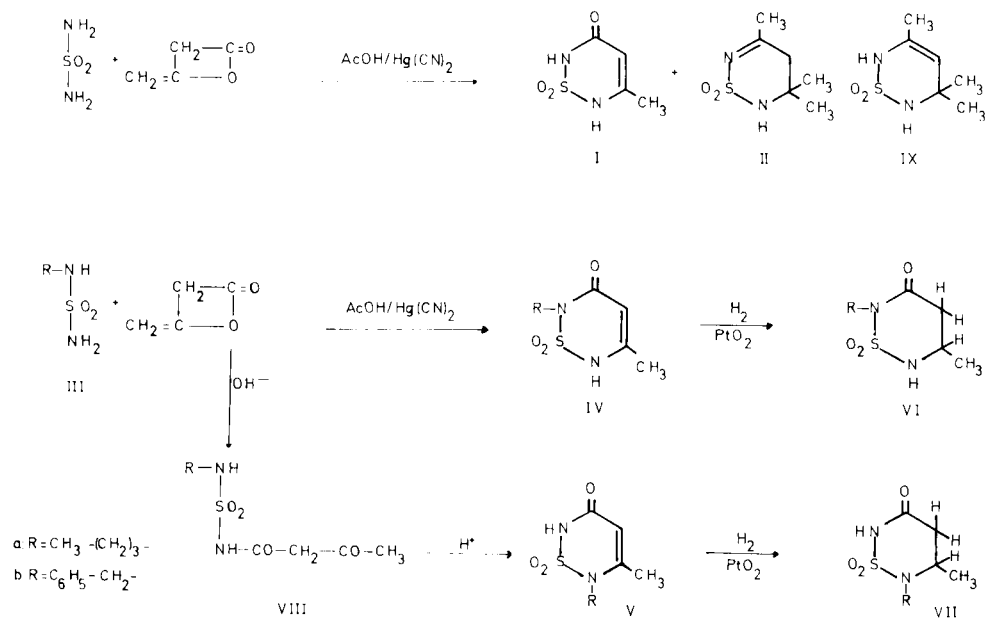
The reaction of *N*-*n*-butyl and *N*-benzylsulfamides with diketene in acetic acid solution in the presence of mercuric cyanide as a catalyst, afforded the corresponding 5-methyl-2-substituted-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-dioxides. The reaction of the above mentioned sulfamides with diketene in an aqueous alkaline medium resulted in the isolation of the corresponding *N*-acetoacetyl-*N'*-substituted-sulfamides, which were then converted into 5-methyl-6-substituted-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-dioxides. Catalytic hydrogenation of the 5-methyl-2- and 6-*n*-butyl-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-dioxides furnished the corresponding dihydro-derivatives. The structures of the isomeric 1,2,6-thiadiazine 1,1-dioxide derivatives obtained were assigned on the basis of nmr spectroscopic studies.

In a previous paper (2) we have reported that treatment of sulfamide with diketene in aqueous sodium hydroxide solution leads to 5-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-dioxide (1) an *S*-dioxo analog of 6-methyluracil wherein a sulfone group replaces the carbonyl group at the 2-position. Subsequently, it was found that the same compound (I) could be obtained when the reaction was conducted in acetic acid solution and in the presence of mercuric cyanide as a catalyst. On the other hand, it has been previously shown (3) that monoalkylureas react with diketene to yield 1- or 3-substituted uracil derivatives, depending on the reaction medium used.

Based on these observations it appeared feasible that under suitable conditions the reaction of monosubstituted sulfamides with diketene would similarly result in the formation of isomeric *N*-substituted 5-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-dioxides. As expected we found that monosubstituted sulfamides III when treated with diketene in an alkaline medium afforded, *via* the corresponding acetoacetyl derivative VIII, 6-substituted-5-methyl-2*H*-1,2,6-thiadiazin-3-(6*H*)one 1,1-dioxides V, whereas on conducting the reaction in acetic acid solution the isomeric 2-substituted-5-methyl-2*H*-1,2,6-thiadiazin-3-(6*H*)-one 1,1-dioxides IV were obtained.

The nmr spectra of isomeric compounds IV and V are nearly identical and they are not useful for structure assignment (4). A specially significant feature of all these 1,2,6-thiadiazine derivatives is the almost instantaneous disappearance of the signal at ~ 4.5 τ (H-4 ring proton) upon addition of deuterium oxide. On the other hand, the ir spectra of these products are very distinctive. 6-Substituted derivatives V showed two intense absorption bands at 1600 and 1540 cm^{-1} (amide bands). This is in contrast to the 2-substituted isomers IV which only showed one absorption band at 1640 cm^{-1} (CO).

In an effort to distinguish between the two types of isomers, the hydrogenated compounds VIa and VIIa were prepared and their nmr spectra studied. Hydrogenation of IVa in ethyl acetate solution with platinum oxide afforded the corresponding dihydro-derivative VIa. Its nmr spectrum (60 MHz, deuteriochloroform) showed, in addition to the *n*-butyl group signals, a doublet at 8.65 τ assigned to the protons of the methyl group at the 5-position. The signals of H-4 ring protons, multiplets centered at 7.50 and 7.27 τ, were observed as the AB part of an ABX system where X is the H-5 ring proton which in turn appeared as a complex multiplet at 6.2 τ ($J_{4,4'}$ = 17.6 Hz, $J_{4,5}$ = 12.4 Hz and $J_{4',5}$ = 3.4 Hz). The NH proton signal consisted of a doublet centered at 4.51 τ (J = 11.2 Hz) which disappeared upon addition of deuterium oxide. If the multiplicity of this last signal were due to the coupling with H-5 ring proton one would anticipate that exchange with deuterium oxide of the NH proton would produce alteration of the H-5 signal. Since simplification of this signal by deuterium exchange of the NH proton is difficult to observe due to the large number of couplings involved, a double-resonance experiment was performed in order to confirm the above assignment. Irradiation of the H-5 multiplet resulted in collapse of the NH doublet (4.51 τ) to a singlet, also a simplification of the doublet of the



methyl group at the 5-position and of the H-4 multiplet was observed.

Catalytic hydrogenation of Va as above gave VIIa. As expected, the nmr spectrum (60 MHz, deuteriochloroform) of VIIa did not show the doublet of the NH proton that was observed in the case of VIa but exhibited a broad singlet at 1.36 τ (NH).

The above results provide conclusive evidence on the structure of the isomeric 1,2,6-thiadiazine 1,1-dioxide derivatives VIa and VIIa and hence proved the structures of the parent compounds IVa and Va, respectively.

As it was to be expected, attempted catalytic hydrogenation under mild conditions of the benzyl derivatives IVb and Vb failed to give the corresponding dihydro-derivatives VIb and VIIb. Instead a complex reaction mixture was obtained which was shown (tlc, chloroform-ethanol-acetic acid 40:2:1) to consist mainly of 5-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-dioxide (I) and its dihydro-derivative (2). Although a direct proof of the structures of IVb and Vb is lacking, structure assignments were made by comparing their uv and ir spectra with those of IVa and Va.

The obtention of the 2-substituted isomers IV involves the initial attack of the substituted nitrogen atom of sulfamide III on diketene, followed by ring closure of the *N*-substituted-*N*-acetoacetylsulfamide so formed. When the reaction of sulfamides III with diketene was carried out in a basic medium the 6-substituted isomers V were produced through the formation of an intermediate *N*-substituted-*N'*-acetoacetylsulfamide VIII which was isolated prior to cyclization.

It should be mentioned that from the reaction of sulfamide and diketene in acetic acid solution an additional compound II was isolated in minor quantity. The structure II was assigned on the basis of the following data. Elemental analysis established its formula as $C_6H_{12}N_2O_2S$. The ir spectrum showed characteristic bands at 3250 cm^{-1} (NH) and 1333, 1163 cm^{-1} (SO_2). The nmr spectrum exhibited singlets at 8.70 τ (*geminal* CH_3), 7.80 τ (CH_3 group), 7.67 τ (methylene ring protons) and a broad singlet at 5.34 τ (NH) which disappeared upon addition of deuterium oxide. The same compound II has been obtained (66.5% yield) and identified by Ouchi and Moeller (5) from the acid-catalyzed reaction between sulfamide and acetone. It is interesting to note that II obtained from both mentioned reactions was identical in every respect (mixed m.p., ir and nmr) with a product prepared (80.5% yield) by Zimmerman and Hotze (6) from sulfamide and mesityl oxide, to which these authors assigned the structure IX. In the light of the reported nmr data, structure IX was ruled out by the absence of any absorption in the region attributable to one olefinic proton. In our case the formation of II as a by-product presumably proceeds from any acetone or mesityl oxide either initially present in the diketene or formed during the reaction by the mercuric cyanide catalyzed decomposition of the diketene (7).

The reactions herein described appear to be a valuable procedure for the synthesis of new nucleosides, starting from available *N*-glycosyl sulfamides (8). This is under investigation in our laboratory.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were obtained with a Perkin-Elmer 137 spectrometer and uv spectra with a Perkin-Elmer 350 spectrophotometer. Nmr spectra were obtained with a Perkin-Elmer R-12 spectrometer at 60 MHz, using TMS as an internal standard.

5-Methyl-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-Dioxide (I) and 3,3,5-Trimethyl-2*H*-1,2,6-thiadiazine 1,1-Dioxide (II).

To a suspension of 4.8 g. (0.05 mole) of sulfamide dried over phosphorus pentoxide and 0.2 g. (0.8 mole) of mercuric cyanide in 20 ml. of glacial acetic acid was added 8 ml. of freshly distilled diketene. The mixture was allowed to stand at room temperature until an exothermic reaction started and the mixture was then gently warmed until the sulfamide dissolved. After cooling, the insoluble solid was removed by filtration. The mother liquor was evaporated under reduced pressure and the residue was dissolved in water. Water was removed under reduced pressure and the process of water addition and evaporation was repeated until the acetic acid was completely eliminated. Alcohol was added and the insoluble material was removed by filtration. The filtrate was evaporated under reduced pressure and the crude residue was chromatographed on a silica gel (Merck) column, using ethyl acetate-petroleum ether (1:1) as eluent. The first fractions afforded I (22% yield), m.p. 173-174° (from nitromethane) which was identified by comparison with an authentic sample (2). Subsequent fractions afforded II (~1% yield), m.p. 143-144° (from ethanol). This compound was identical (mixed m.p., ir and nmr) with the product obtained following the reported procedures (5,6).

5-Methyl-2-*n*-butyl-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-Dioxide (IVa).

This compound was prepared by reaction of *N*-butylsulfamide (0.05 mole) (8), mercuric cyanide (0.8 mole) and diketene (8 ml.) in 20 ml. of glacial acetic acid. The above procedure was repeated, except that ethanol treatment was omitted. Recrystallization from ethyl acetate-cyclohexane afforded pure IVa (16.5% yield), m.p. 109-110°; ir (nujol): 1640 (CO), 1100-1200 cm^{-1} (SO_2); nmr (DMSO-d_6, τ): 4.52 (s, H-4 ring proton), 6.3 (t, $CH_3(CH_2)_2CH_2$ N<), 7.95 (s, CH_3 group at 5-position); uv λ max (ethanol): 258 mμ (ϵ, 7,350).

Anal. Calcd. for $C_8H_{14}N_2O_3S$: C, 44.03; H, 6.42; N, 12.84. Found: C, 44.27; H, 6.56; N, 12.57.

5-Methyl-2-benzyl-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-Dioxide (IVb).

The synthesis of this compound was accomplished as before starting from *N*-benzylsulfamide (0.05 mole) (9). After removal of the acetic acid the resulting oily residue was left at room temperature for 5 days. The solid obtained was recrystallized from chloroform-petroleum ether to give IVb (27% yield), m.p. 172-173°; ir (nujol): 1640 cm^{-1} (CO), 1100-1200 cm^{-1} (SO_2); nmr (DMSO-d_6, τ): 2.72 (s, 5H phenyl group), 4.52 (s, H-4 ring proton), 5.12 (s, $ArCH_2N$<), 7.92 (s, CH_3 group); uv λ max (ethanol); 255 mμ (ϵ, 8,880).

Anal. Calcd. for $C_{11}H_{12}N_2O_3S$: C, 52.38; H, 4.76; N, 11.11. Found: C, 52.03; H, 4.80; N, 11.05.

N-*n*-Buthyl-*N'*-acetoacetylsulfamide (VIIIa).

To a solution of 2 g. (0.05 mole) of sodium hydroxide in 45 ml. of water was added 7.6 g. (0.05 mole) of *N*-*n*-butylsulfamide. To the stirred and ice-cooled mixture was then slowly added 5 g. (0.06 mole) of diketene while maintaining the temperature at 10-15°. The mixture was stirred at room temperature for 2 hours and extracted several times with ethyl acetate. The solid obtained after evaporation of the ethyl acetate was recrystallized from ethyl acetate to give 8.3 g. (70% yield) of VIIIa, m.p. 123-125°, ir (nujol): 1720 (CO), 1680 (*CO*-NH), 1100-1200 cm^{-1} (SO_2); nmr (DMSO-d_6, τ): 2.38 (m, -N*H*-), 6.51 (s, CO-*CH*$_2$-CO, interchange with deuterium oxide), 7.83 (s, *CH*$_3$-CO).

Anal. Calcd. for $C_8H_{16}N_2O_4S$: C, 40.67; H, 6.77; N, 11.86. Found: C, 40.77; H, 6.83; N, 12.04.

5-Methyl-6-*n*-butyl-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-Dioxide (Va).

A solution of 0.8 g. (0.0035 mole) of VIIIa in 10 ml. of ethanolic hydrogen chloride (absolute ethanol saturated with hydrogen chloride at 0°) was allowed to stand 1.5 hours at 0°. The solvent was removed under reduced pressure. The residue was recrystallized from benzene-cyclohexane to give 0.55 g. (75% yield), m.p. 129-130°; ir (nujol): 1595 and 1542 (amide bands), 1100-1200 cm^{-1} (SO_2); nmr (DMSO-d_6, τ): 4.47 (s, H-4 ring proton), 6.23 (t, CH_3 $(CH_2)_2$ CH_2N<), 7.72 (s, CH_3 group at 5-position); uv λ max (ethanol): 295 mμ (ϵ, 7,750).

Anal. Calcd. for $C_8H_{14}N_2O_3S$: C, 44.03; H, 6.42; N, 12.84. Found: C, 44.14; H, 6.48; N, 13.01.

N-Benzyl-*N'*-acetoacetylsulfamide (VIIIb).

This compound was obtained by the procedure above described for VIIIa, starting from 4.8 g. (0.05 mole) of *N*-benzylsulfamide, m.p. 134-135° (from ethyl acetate-petroleum ether), yield 55%; ir (nujol): 1696 (CO), 1100-1200 cm^{-1} (SO_2), nmr (DMSO-d_6, τ); 1.71 (m, -N*H*-), 5.83 (d, -*CH*$_2$-NH-), 6.58 (s, CO-*CH*$_2$-CO) 7.84 (s, *CH*$_3$-CO).

Anal. Calcd. for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.18; N, 10.36. Found: C, 48.67; H, 5.10; N, 10.53.

5-Methyl-6-benzyl-2*H*-1,2,6-thiadiazin-3(6*H*)one 1,1-Dioxide (Vb).

This compound was prepared from VIIIb (0.65 g., 0.003 mole) in a similar manner as described for Va; m.p. 177-179° (from ethyl acetate-petroleum ether); yield, 41%; ir (nujol): 1593 and 1553 (amide bands), 1100-1200 cm^{-1} (SO_2); nmr (DMSO-d_6, τ): 2.64 (s, 5H, phenyl group), 4.39 (s, H-4 ring proton) 4.92 (s, Ar CH_2N<), 7.89 (s, CH_3 group); uv λ max (ethanol): 293 mμ (ϵ, 7,870).

Anal. Calcd. for $C_{11}H_{12}N_2O_3S$: C, 52.38; H, 4.76; N, 11.11. Found: C, 52.48; H, 4.72; N, 11.36.

5-Methyl-6-*n*-butyldihydro-2*H*-1,2,6-thiadiazin-3(4*H*)one 1,1-Dioxide. (VIIa).

Catalytic hydrogenation of Va (1 g.) in ethyl acetate solution with platinum oxide at room temperature and 3 atm afforded 0.93 g. of VIIa, (92% yield), m.p. 114-115° (from ethyl acetate-petroleum ether); ir (nujol): 1684 (CO), 1100-1200 cm^{-1} (SO_2); nmr (deuteriochloroform, τ): 1.36 (m, >NH), 5.96 (b, m, H-5 ring proton), 7.43 (m, 2H, H-4 ring protons), 8.6 (d, 3H, 5-CH_3 group).

Anal. Calcd. for $C_8H_{16}N_2O_3S$: C, 43.63; H, 7.27; N, 12.72. Found: C, 43.80; H, 7.37; N, 12.90.

5-Methyl-2-*n*-butyldihydro-2*H*-1,2,6-thiadiazin-3(4*H*)one 1,1-Dioxide (VIa).

Catalytic hydrogenation of IVa (1 g.) in a similar manner as described above afforded 0.89 g. of VIa in 89% yield, m.p. 79-80° (from cyclohexane); ir (nujol): 1670 (CO), 1100-1200 cm^{-1} (SO_2).

Anal. Calcd. for $C_8H_{16}N_2O_3S$: C, 43.63; H, 7.27; N, 12.72. Found: C, 43.86; H, 7.27; N, 12.72.

Acknolwedgments.

The authors wish to thank Prof. M. Lora-Tamayo for his encouragement and Dr. M. Rico for his assistance in the interpretation of the nmr spectra. This work was supported by a grant from the Fondo Nacional para el Fomento de la Investigación.

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