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Received November 24, 1980

Reactivity towards alkylating agents in relation to the capacity to bind sodium ions of 1,2,6-thiadiazine 1,1-dioxide derivatives is described. The compounds studied are: **1**, 4-nitro-, **2**, 4-cyano-, **3**, 4-ethoxycarbonyl-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide and **4**, 3-amino-4-cyano-6*H*-1,2,6-thiadiazine 1,1-dioxide. Methylation with dimethyl sulfate of 4-nitro- and 4-cyanothiadiazines **1** and **2**, which show the capacity to bind sodium ions, takes place regioselectively at position 2, whilst the thiadiazines which lack this feature (**3** and **4**) are methylated at 2 and 6, and 6 respectively. On using diazomethane, in the absence of alkaline ions, no selectivity was observed. Glycosidation reactions of **1**, **3** and **4** have also been carried out. The structure of the newly synthesized compounds are discussed on the basis of their analytical and spectroscopic data.

Continuing with our studies on the preparation and reactivity of 2-*S*-dioxo isosteres of pyrimidines and purines (1), we now wist to report our results on the selective alkylation and glycosidation of some of these derivatives. The chelating effect (2) observed in some of these thiadiazine compounds results in water soluble but non ionizable salts which differ in their reactivity with that of non-chelating thiadiazines.

In the course of the preparation of 4-substituted 1,2,6-thiadiazine 1,1-dioxides **1**, **2**, **3** and **4** (3), it was found that some of these compounds show a great tendency to bind alkaline ions. Exceptionally, resin exchange with Amberlite IR-120 H⁺ does not release sodium from the sodium compounds **1a** and **2a**. Moreover after treatment of **2a** with boiling silver nitrate and hydrogen sulfide the starting sodium compound **2a** was recovered unchanged (3). These 4-substituted thiadiazine sodium complexes **1a** and **2a** were prepared by condensation reactions between sulfamide and the corresponding ethoxymethylene derivatives in the presence of sodium ethoxide. When the condensations were carried out in potassium isopropoxide/methanol, after treatment with acetic acid the corresponding dipotassium salts were obtained. Treatment of these salts with hydrochloric acid afforded the corresponding monopotassium salts **1b** and **2b**. The free compounds may

be obtained from the latter by resin (Amberlite IR-120 H⁺) exchange or by extraction with ethyl acetate in acid medium.

The structures of these heterocycles as well as of their sodium and potassium salts have been studied by X ray diffraction techniques (4). The results show significant changes in the electronic distribution of both the free thiadiazines and their corresponding salts. This fact, together with the already mentioned irreversibility of the chelate formation suggested different behaviour towards alkylating reagents. Thus, we have studied the reactivity of those thiadiazine derivatives which showed the chelating effect (**1** and **2**), as well as of those which did not have this feature (**3** and **4**).

Methylation reactions of compounds **1**, **2**, **3** and **4** were performed and only in the case of the 4-ethoxycarbonyl-thiadiazine **3** were the two possible *N*-methyl derivatives isolated. The reaction was carried out with dimethyl sulfate both in sodium hydroxide and bicarbonate to yield the *N*-6 and *N*-2 methyl derivatives **5** and **6** in a 1:2 ratio, evaluated from the ¹H nmr spectrum of the reaction mixture. Both isomers had very close Rf values and had to be separated by crystallization, the one which crystallized first, being the *N*-6 isomer **5**. The structure of **5** was established on the basis of ¹³C nmr spectroscopy by com-
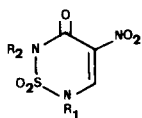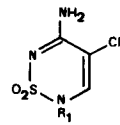

1 . R₁ = R₂ = H
8 . R₁ = H, R₂ = CH₃
15 . R₁ = No, R₂ = X
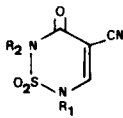
2 . R₁ = R₂ = H
9 . R₁ = H, R₂ = CH₃
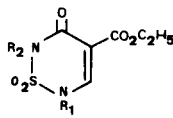
3 . R₁ = R₂ = H
5 . R₁ = CH₃, R₂ = H
6 . R₁ = H, R₂ = CH₃
11 . R₁ = X, R₂ = H
13 . R₁ = Y, R₂ = H

4 . R₁ = H
7 . R₁ = CH₃
12 . R₁ = X
14 . R₁ = Y

X = 2, 3, 4, 6, – tetra – O – acetyl – ß – D – glucopyranosyl –

Y = 2, 3, 5, – tri – O – benzoyl – ß – D – ribofuranosyl –

Table I

^{13}C nmr Chemical Shifts (ppm) and Coupling Constants (Hz) for Compounds **3** and **5** in DMSO at 25.2 MHz using TMS as Internal Standard

Compound No.	C_3	C_4	C_5	C_7	C_8	C_{10}
3	165.15 (d)	92.24 (d)	153.17 (d)	164.57 (t)	59.96 (t,q)	—
5	155.08 (d)	94.28 (s)	155.68 (d,q)	162.93 (t)	60.38 (t,q)	36.08 (t,d)
Δ C (a)	0.93	2.04	2.51	−1.64	0.42	−0.02
	$J_{C_3\text{-}H_5}$ (b)	$J_{C_5\text{-}H_5}$	$J_{C_5\text{-}H_{10}}$	$J_{C_{10}\text{-}H_{10}}$	$J_{C_{10}\text{-}H_5}$	
3	9.0	182.0	—	—	—	
5	9.5	184.4	3.2	143.6	4.08	

(a) Δ C = C (methyl thiadiazine **5**)-C (thiadiazine **3**); positive values are downfield. (b) Tentatively we suggest that C_3 is coupled with H-5 by comparison of the value of $J_{C_3\text{-}H_5}$ = 9.5 Hz with that of the corresponding $J_{C_4\text{-}H_6}$ = 10.3 Hz in uridine (12) (see Figure 2).

parison with the non methylated thiadiazine **3**. The ^{13}C nmr parameters of compounds **3** and **5** are collected in Table I.

In the ^{13}C nmr spectrum of compound **3** the signal corresponding to the C-5 appears as a doublet, whilst in the N-6 methyl derivative **5** it appears as two quartets due to the long-range coupling C_5-H_{10}. Likewise, the quartet corresponding to the methyl group appears split due to the longrange coupling C_{10}-H_5, indicating that the methyl group is attached to the N-6 position. Besides, the coupling constant $J_{C_5\text{-}H_{10}}$ (3.2 Hz) falls in the same interval as the corresponding $J_{C_6\text{-}H_1'}$ (3.7 Hz) of uridine (5), as can be seen in Figure 2.

URIDINE

$^3J\,(C_6\text{-}H_1')$ = 3.7 Hz
$^3J\,(C_4\text{-}H_6)$ = 10.3 Hz

5

$^3J\,(C_5\text{-}H_{10})$ = 3.2 Hz
$^3J\,(C_3\text{-}H_5)$ = 9.5 Hz
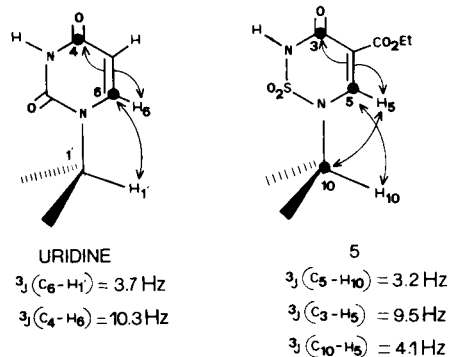$^3J\,(C_{10}\text{-}H_5)$ = 4.1 Hz

Figure 2

These results allow us to establish that the chemical shift of the methyl group at N-6 is that which appears at δ 3.6 in the ^{1}H nmr spectrum, whilst that of the N-2 at δ 3.1, which is in full agreement with previous results obtained for other 3-oxo-thiadiazine 1,1-dioxides (6).

Treatment of **4** with dimethyl sulfate both in sodium hydroxide and bicarbonate afforded only the N-6 methyl derivative **7**. The methyl group appeared in the ^{1}H nmr spectrum at δ 3.6 in agreement with the results mentioned above.

On the other hand, when the thiadiazine derivatives showing the chelating effect **1** and **2** were made to react with dimethyl sulfate in alkaline medium only the corresponding N-2 methyl derivatives **8** and **9** were obtained. Treatment of **1** both in sodium or potassium hydroxide or bicarbonate afforded, in every case, only the N-2 methyl derivative **8** which was also isolated as its potassium and sodium salts; both salts yield the free methyl derivative **8** upon resin exchange. The value of the ^{1}H nmr chemical shift of the N-methyl group is similar to that previously found for **6** and corresponds with the expected value for a N-2 substitution.

In similar reactions, **2** afforded also an N-2 methyl derivative **9** which was also isolated as its potassium salt. In the reaction of **2** with dimethyl sulfate performed in sodium bicarbonate 4-cyano-3-methoxy-6-methyl-1,2,6-thiadiazine 1,1-dioxide (**10**) was also isolated as a minor component.

Thiadiazines **1** and **2** were also made to react with diazomethane but these turned out to be complex reaction mixtures. However, the ^{1}H nmr spectra of them showed that no methylation had taken place at position 2. In the case of **1** an O-3, N-6 dimethyl derivative with similar nmr features as **10** could be separated.

In addition, benzylation was attempted with benzyl chloride in the usual manner and using phase transfer catalysts (7) but no benzyl thiadiazine could be obtained. However, this is not surprising since N- and O-benzylation are not favoured in the thiadiazine ring (6,8).

In order to study also the influence of the chelating effect on nucleoside preparation, glycosidation reactions were carried out. Thiadiazines **3** and **4** were made to react with suitable sugar halides according to the mercuric cyanide-nitromethane procedure (9). Thus, the corresponding N-6 glucosyl **11** and **12** and N-6 ribosyl derivatives **13** and **14** were obtained. On the other hand, glycosidation reactions of thiadiazines **1** and **2** showed many difficulties. Attempts using the silylated thiadiazines

and trifluoroboride etherate as catalyst with peracetylated sugars (10) also turned out to be unsuccessful. When the sodium compound **1a** was made to react with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide following the mercuric cyanide-nitromethane procedure an *N*-2 glycosyl derivative **15** which still had sodium bound (checked by a.a. spectrophotometry) could be isolated.

The site of glycosidation was established by comparing the uv spectra of the nucleosides with those of the corresponding methyl derivatives and other substituted thiadiazines (11). The configuration was established as β on the basis of mechanistic considerations (12) and, in some cases, checked in the value of the coupling constants $J_{1'-2'}$.

Further work is in progress to extend this procedure of selective glycosidation to the case of other heterocycles.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. ¹H nmr spectra were obtained on a Perkin-Elmer R-12 instrument. Chemical shifts are given as parts per million (ppm) downfield from tetramethylsilane in δ units and coupling constants are reported in hertz. ¹³C nmr spectra were determined on a Varian XL-100-15 instrument at 25.2 MHz. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, uv spectra were recorded on a Perkin-Elmer 350 and 402 spectrophotomers.

Methylation Reactions.

To a solution of 0.01 mole of the corresponding either free thiadiazine or its sodium or potassium salt in 20 ml. of 1*N* sodium or potassium hydroxide (method a) or 1*N* sodium or potassium bicarbonate (method b) dimethyl sulfate (0.02 mole) was added dropwise. The reaction mixture was stirred at room temperature overnight.

4-Ethoxycarbonyl-6-methyl-2*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (**5**) and 4-Ethoxycarbonyl-2-methyl-6*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (**6**) (Method a).

The cooled reaction mixture was brought to *p*H 1 with concentrated hydrochloric acid to give a white precipitate which was a 1:2 mixture of **5** and **6** (overall yield 85%). Recrystallization from ethylacetate/petroleum ether afforded pure **5** as white rods, m.p. 184-185°; uv (water): λ max 220 and 282 nm; ¹H nmr (DMSO-d₆): δ 8.6 (s, 1H, H-5), 6.2 (bm, 1H, NH), 4.3 (q, 2H, C*H*₂-CH₃), 3.6 (s, 3H, CH₃), 1.3 (t, 3H, CH₂-C*H*₃).

Anal. Calcd. for C₇H₁₀N₂O₅S: C, 35.89; H, 4.27; N, 11.96. Found: C, 36.15; H, 4.42; N, 12.35.

The filtrate left after several crystallizations was evaporated to dryness and recrystallized from methanol to give pure **6**, m.p. 178-179°; uv (water): λ max 220 nm (ε, 9,900), 285 nm (ε, 10,200); ¹H nmr (DMSO-d₆): δ 8.2 (s, 1H, H-5), 4.15 (q, 2H, C*H*₂-CH₃), 3.1 (s, 3H, CH₃), 1.25 (t, 3H, CH₂-C*H*₃).

Anal. Calcd. for C₇H₁₀N₂O₅S: C, 35.89; H, 4.27; N, 11.96. Found: C, 35.59; H, 4.19; N, 11.77.

3-Amino-4-cyano-6-methyl-1,2,6-thiadiazine 1,1-Dioxide (7) (Method b).

The precipitate which had appeared was filtered off and recrystallized from water/methanol to give **7** as white crystals (62%), m.p. 281-282°; uv (water): λ max 294 (ε, 13,000); ¹H nmr (DMSO-d₆): δ 8.5 (s, 1H, H-5), 8.2 (bm, 2H, NH₂), 3.5 (s, 3H, CH₃).

Anal. Calcd. for C₅H₆N₄O₂S: C, 32.35; H, 3.22; N, 30.10. Found: C, 32.25; H, 3.46; N, 30.24.

2-Methyl-4-nitro-6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide (**8**) (Method b).

The solid precipitate which had appeared after cooling was collected,

washed with ethanol and recrystallized twice from water, to give the corresponding sodium **8a** (22%) or potassium salts **8b** (17%) depending on the reaction mixture used.

Compound **8a**.

This compound had m.p. > 300° dec.; uv (water): λ max 265 nm (ε, 3,400), 331 nm (ε, 7,800); ¹H nmr (DMSO-d₆): δ 8.8 (s, 1H, H-5), 3.1 (s, 3H, CH₃).

Anal. Calcd. for C₄H₄N₃O₅S·Na: C, 20.96; H, 1.74; N, 18.34. Found: C, 20.95; H, 1.95; N, 17.91.

Compound **8b**.

This compound had m.p. −300° dec; uv (water): λ max 267 nm (ε, 4,800), 334 nm (ε, 15,600); ¹H nmr (DMSO-d₆): δ 8.9 (s, 1H, H-5), 3.15 (s, 3H), CH₃).

Anal. Calcd. for C₄H₅N₃O₅S: C, 23.18; H, 2.41; N, 20.29. Found: C, 23.36; H, 2.39; N, 20.52.

4-Cyano-2-methyl-6*H*-1,2,6-thiadiazin-3-one (**9**) (Method b).

The solid precipitate which had appeared after performing the reaction in 1*N* potassium bicarbonate was recrystallized twice from water to give its monopotassium salt **9b** (20%), m.p. > 300° dec.; uv (water): λ max 292 nm (ε, 10,200); ¹H nmr (DMSO-d₆): δ 7.8 (s, 1H, H-5), 3.1 (s, 3H, CH₃).

Anal. Calcd. for C₅H₄N₃O₃SK: C, 26.66; H, 1.77; N, 18.66. Found: C, 26.81; H, 1.59; N, 18.24.

Compound **9** was obtained from **9b** by resin exchange (Amberlite IR-120 H⁺) m.p. 172-173°; uv (water): λ max 283 nm.

Anal. Calcd. for C₅H₅N₃O₃S: C, 33.08; H, 2.67; N, 22.45. Found: C, 32.82; H, 3.00; N, 22.25.

4-Cyano-3-methoxy-6-methyl-1,2,6-thiadiazine 1,1-dioxide (**10**) (Method b).

From the reaction mixture **10** could be isolated (5%), m.p. (water/methanol) 183-184°; uv (water): λ max 288 nm; ¹H nmr (deuteriochloroform): δ 7.75 (s, 1H, H-5), 4.15 (s, 3H, O-CH₃), 3.69 (s, 3H, N-CH₃).

Anal. Calcd. for C₆H₇N₃O₃S: C, 35.82; H, 3.48; N, 20.89. Found: C, 35.44; H, 3.74; N, 20.99.

Glycosidation Reactions.

A mixture of the corresponding thiadiazine (0.005 mole) and mercuric cyanide (2.52 g., 0.01 mole) was added to nitromethane (500 ml.) and dried by azeotropic distillation. The suitable sugar halide (0.005 mole), either 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide was added dropwise to the mixture during 30 minutes with continuous gradual distillation of nitromethane. The mixture was then boiled for 4 hours with continuous, gradual distillation of nitromethane and thereafter evaporated *in vacuo*. The syrupy residue was extracted with chloroform and the extract was washed with 30% aqueous potassium iodide (2 × 50 ml.) and water (50 ml.), dried with sodium sulfate, concentrated and worked up as indicated in each case.

4-Ethoxycarbonyl-6-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (**11**).

The residue was purified by preparative tlc (solvent:chloroform: methanol:acetic acid 40:2:1) giving pure **11** as a glass (1.76 g., 64%); uv (ethanol): λ max 280 nm (ε, 20,200); ¹H nmr (deuteriochloroform): δ 8.16 (s, 1H, H-5), 5.05-5.50 (m, 3H, H-1′, H-2′, H-3′).

Anal. Calcd. for C₂₀H₂₆N₂O₁₄S: C, 43.63; H, 4.72; N, 5.09. Found: C, 43.40; H, 4.95; N, 4.78.

3-Amino-4-cyano-6-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,6-thiadiazine 1,1-Dioxide (**12**).

Due to the insolubility of this compound it was necessary to work with an acetone-chloroform mixture and in the course of the usual work-up **12** fell out from this mixture, and was recrystallized from nitromethane, m.p. 214-215°; uv (ethanol): λ max 283 nm (ε, 14,000); ¹H nmr

(DMSO-d_6): δ 8.88 (s, 1H, H-5), 5.76 (d, J = 9 Hz, 1H, H-1').

Anal. Calcd. for $C_{18}H_{22}N_4O_{11}S$: C, 43.03; H, 4.38; N, 11.15; S, 6.37. Found: C, 42.93; H, 4.24; N, 10.93; S, 6.65.

4-Ethoxycarbonyl-6-(2,3,5-tri-*O*-benzoyl-β-ᴅ-ribofuranosyl)-2*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (13).

The residue was crystallized twice from ethanol to give pure **13** (1.62 g. 60%), m.p. 150-151°; uv (ethanol): λ max 229 nm (ε, 40,700), 284 nm (ε, 10,100); ¹H nmr (deuteriochloroform): δ 8.55 (s, 1H, H-5), 5.98 (d, J = 4 Hz, 1H, H-1').

Anal. Calcd. for $C_{32}H_{28}N_2O_{12}S$: C, 57.83; H, 4.22; N, 4.22; S, 4.81. Found: C, 57.55; H, 4.15; N, 4.09; S, 4.52.

3-Amino-4-cyano-6-(2,3,5-tri-*O*-benzoyl-β-ᴅ-ribofuranosyl)-1,2,6-thiadiazine 1,1-Dioxide (14).

The experimental procedure was the same as that described for **12**. At the end, **14** was recrystallized from acetone/ethanol, m.p. 197-198°; uv (ethanol): λ max 229 nm (ε, 14,300), 284 (ε, 6,600); ¹H nmr (DMSO-d_6): δ 8.70 (s, 1H, H-5), 6.20 (s, 1H, H-1').

Anal. Calcd. for $C_{30}H_{24}N_4O_9S$: C, 58.44; H, 3.82; N, 9.08. Found: C, 58.55; H, 3.63; N, 8.83.

Sodium Salt of 4-Nitro-2-(2,3,4,6-tetra-*O*-acetyl-β-ᴅ-glucopyranosyl)-6*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (15).

Starting from sodium salt **1a**. The residue was purified by preparative tlc (solvent:chloroform:methanol:acetic acid 40:2:1). The slower-running band was collected to give pure **15** as a yellow glass (32%); uv (water): λ max 245 nm (ε, 6,300), 310 nm (ε, 7,000); ¹H nmr (DMSO-d_6): δ 8.75 (s, 1H, H-5), 5.5 (d, J = 6 Hz, 1H, H-1').

Anal. Calcd. for $C_{17}H_{21}N_3O_{14}SNa$: C, 37.43; H, 3.67; N, 7.70. Found: C, 37.40; H, 3.78; N, 7.39.

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