

P. Goya and M. Stud

Instituto de Química Médica, Juan de la Cierva, 3, Madrid-6, Spain

Received November 28, 1977

Preparation of *N*-(tetrahydropyran-2-yl)sulfamide, *N*-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)sulfamide and *N*-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)sulfamide is described. Reactions with diketene, in the presence of pyridine, yielded *N*-sulfamoyl-2,6-dimethyl-4-pyrone-3-carboxamide derivatives.

J. Heterocyclic Chem., 15, 477 (1978)

In previous work, we have studied the synthesis of *S*-dioxo analogs of naturally occurring heterocyclic systems (2), and related nucleosides (3), which could act as anti-metabolites. We now wish to report the preparation of glycosylsulfamides, which could be useful starting materials in order to obtain analogs of nucleosides or glycosyl-nitrosoureas. The behaviour of these sulfamides against diketene, was somewhat different to that shown by other monosubstituted sulfamides, as previously reported (1).

Although glucopyranosylsulfamide had already been described (4), we report, in the present paper, a new method for its obtention as well as for ribofuranosyl- and tetrahydropyransylsulfamide. The procedure described by Hatt, *et al.* (4), for the preparation of tetra-*O*-acetylglucopyranosylsulfamide leads to the glucopyranosylsulfamide which has to be further acetylated.

N-(Tetrahydropyran-2-yl)sulfamide (II) was obtained by reaction of 3,4-dihydro-2*H*-pyrane and sulfamide in the presence of trifluoroacetic acid as catalyst. *N*-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)sulfamide (III) and *N*-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)sulfamide (IV) were prepared from sulfamide and the corresponding glycosyl halides following the mercuric cyanide-nitromethane procedure (5) used for the synthesis of nucleosides. In both

cases, the final reaction products had to be separated by preparative chromatography. For purifying tetra-*O*-acetylglucopyranosylsulfamide (III) we took advantage of the fact that this compound separates from a solution in chloroform, in a molecular addition compound (4). Pure compound III was obtained by recrystallization of this complex from hot water.

It is worth mentioning that all our attempts to extend the mercuric cyanide-nitromethane procedure to the case of urea, which would lead to the *N*-glycosylureas, had no success.

The H-1 nmr spectra of these three compounds had similar features. Thus the NH₂ group appeared in all of them, within the range of δ 5-6.5, whilst the doublet at δ 6.2-7.8 was assigned to the NH coupled with the "anomeric proton" ($J_{CH-NH} \sim 9$ Hz), as could be demonstrated by addition of deuterium oxide and decoupling experiments in compound II. The value of the coupling constant $J_{2-3'} = 8.5$ Hz of racemic compound II indicated that the tetrahydropyranyl rest adopted, preferentially, the chair conformation where the sulfamido rest is at the equatorial position. The coupling constants $J_{1'-2'}$ could not be measured either for III or IV; nevertheless, compound III was identified as the β anomer since III was

Scheme I

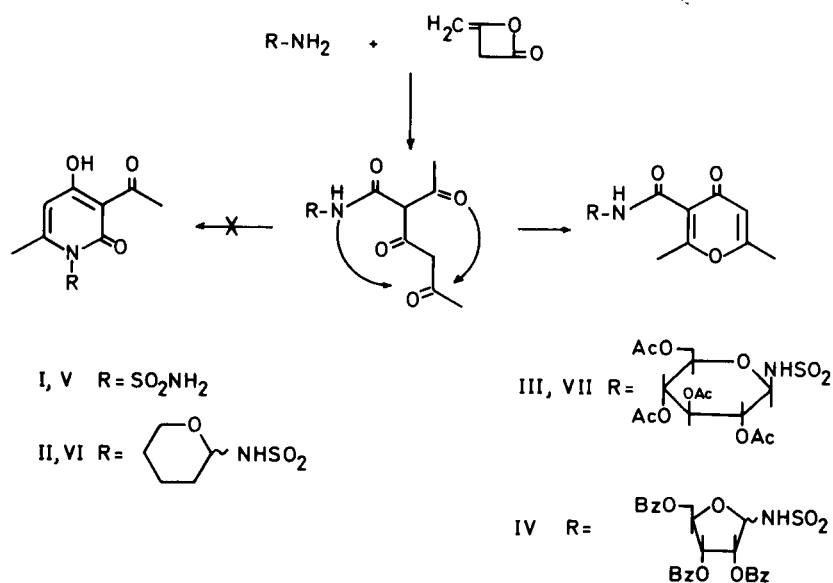


Table I
Spectroscopic Data of 2,6-Dimethyl-4-pyrone-3-carboxamide Derivatives

Compound	Ir (nujol, ν) cm^{-1}		uv		^1H nmr (DMSO- d_6 , δ)			
	C=O amide	C=O pyrone	λ max (Ethanol) nm	ϵ	CO-NH	H-5	CH ₃ -2	CH ₃ -6
V	1,690	1,660	247	8,600	12.70	6.45	2.68	2.35
VI	1,700	1,660	245	7,900	12.30	6.32	2.55	2.25
VII	1,700	1,650	247	--	12.40	6.40	2.53	2.35

identical in all respects to that reported by Hatt (4).

We had previously described that sulfamide (6) and monosubstituted sulfamides (I) reacted with diketene to give 1,2,6-thiadiazin-3-one 1,1-dioxide derivatives. It was also known, that the reaction of amines (7) with diketene, could give, in addition to the acetoacetamides, 4-pyrone and 4-pyridone derivatives, when carried out in the presence of a basic catalyst.

When sulfamides I, II and III reacted with an excess of diketene, in the presence of pyridine, the 4-pyrone derivatives V, VI and VII were obtained. The reaction of II, yielded V in addition to VI, the former by loss of the tetrahydropyran-2-yl rest from VI. The formation of only the 4-pyrone derivatives could be explained on the basis of the bulkiness and acidity of the starting sulfamides, as shown in Scheme I. In addition, we have found out that the reaction conditions are, to a large extent, also responsible for the obtention of 4-pyrones, since in the reaction of sulfamide with diketene, under these conditions, the formation of the 4-pyrone (V) competed with that of 5-methyl-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide (6).

In an excellent piece of work (8), Kato has established a criterion for distinguishing between isomeric 4-pyrones and 4-pyridones, derived from several aminopyrimidines, by means of their mass fragmentation. Thus, the intense peaks at m/e 151, 109 and 67, shown by compound V are coincident with those assigned by Kato for the 4-pyrone-3-carboxamides. On the basis of this assignment, Kato has reported different ^1H nmr and ir data for 4-pyrone and 4-pyridone derivatives, which together with their uv spectra, have been very useful in establishing the 4-pyrone structure also for VI and VII. The spectroscopic data for V, VI and VII are summarized in Table I.

It seems likely that no anomerization nor any configurational change took place in the course of the formation of the 4-pyrone-3-carboxamides. Besides, the value of the coupling constant ($J_{2-\text{NH}} = 9.5$ Hz) of *N*-[*N'*-(tetrahydropyran-2-yl)sulfamoyl]-2,6-dimethyl-4-pyrone-3-carboxamide (VI) suggested that the sulfamoyl rest retained the same disposition, as in the starting material.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured

on a Perkin-Elmer 257 spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12 and a Varian XL-100 spectrometers with TMS as internal standard. Ultra-violet spectra were recorded on a Perkin-Elmer 350 and 402 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Mass spectra were run on a Hitachi Perkin-Elmer RMV-GMG spectrometer.

N-(Tetrahydropyran-2-yl)sulfamide (II).

A solution of 1.92 g. (0.02 mole) of sulfamide and 1.68 g. (0.02 mole) of 3,4-dihydro-2*H*-pyrane in 50 ml. of ethyl acetate with a catalytic amount of trifluoroacetic acid, was refluxed gently for 6 hours. The reaction mixture was concentrated to dryness *in vacuo* and the residue recrystallized from ethanol yielding 1.3 g. (40%), m.p. 73-74°; ^1H nmr (DMSO- d_6 , δ): 7.40 (d, 1H, NH, $J_{2-\text{NH}} = 9.5$ Hz), 6.28 (s, 2H, NH₂), 4.50 (t, 1H, H-2, $J_{2-3'} = 8.5$ Hz).

Anal. Calcd. for C₅H₁₂N₂O₃S: C, 33.33; H, 6.71; N, 15.55; S, 17.61. Found: C, 33.72; H, 6.97; N, 15.32; S, 17.89.

N-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)sulfamide (III).

A mixture of 1.92 g. (0.02 mole) of sulfamide and 6 g. (0.023 mole) of mercuric cyanide was added to 300 ml. of nitromethane, and dried by azeotropic distillation. Tetra-*O*-acetyl- α -D-glucopyranosyl bromide (4.93 g., 0.012 mole) was added, dropwise to the mixture during 30 minutes with continuous, gradual distillation of nitromethane. The mixture was kept distilling for 4 hours and, thereafter, evaporated *in vacuo*. The syrupy residue was extracted with chloroform, and the extracts washed with 30% aqueous potassium iodide (2 x 50 ml.) and water (50 ml.), dried over sodium sulfate and concentrated. It was then applied to an 80 g. column of silica gel, and the column was eluted with chloroform. Product-containing fractions were concentrated to give a crystalline complex. Recrystallization from hot water gave 1.5 g. (30%) of pure III, m.p. 146-147°; ^1H nmr (DMSO- d_6 , δ): 7.84 (d, 1H, NH, $J_{1'-\text{NH}} = 9$ Hz), 6.51 (s, 2H, NH₂); ir (nujol, ν): 3,700 cm^{-1} (NH₂), 3,300 cm^{-1} (NH).

Anal. Calcd. for C₁₄H₂₂N₂O₁₁S: C, 39.43; H, 5.20; N, 6.57. Found: C, 39.14; H, 5.12; N, 6.46.

N-(2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl)sulfamide (IV).

This compound was prepared from 6.5 g. (0.012 mole) of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (9), in a similar manner as described for III. The crude residue (6 g.) thus obtained was applied to preparative tlc plates (Silica Gel PF₂₅₄ (Merck), 20 x 20 cm; 2 mm thick). The plates were eluted with 40:2:1 (chloroform:ethanol:acetic acid). The slower-moving band was leached from the silica gel with ethanol. Evaporation of the solvent left 1.6 g. (25%) of pure IV as a glass; $[\alpha]_{\text{D}} = +16^\circ$ (c, 0.51, chloroform); uv λ max (ethanol): 231 nm (ϵ , 32,500); ^1H nmr (deuteriochloroform, δ): 6.28 (d, 1H, NH, $J_{1'-\text{NH}} = 10$ Hz), 5.15 (s, 2H, NH₂); ir (nujol, ν): 3,500 cm^{-1} (NH₂).

Anal. Calcd. for C₂₆H₂₄N₂O₉S: C, 57.77; H, 4.47; N, 5.18. Found: C, 57.74; H, 4.61; N, 4.91.

N-(Sulfamoyl)-2,6-dimethyl-4-pyrone-3-carboxamide (V).

To a well-stirred mixture of 0.38 g. (0.004 mole) of sulfamide in 20 ml. of nitromethane and some drops of pyridine, 0.67 g. (0.008 mole) of freshly distilled diketene were added dropwise. The orange solution was stirred at room temperature for 24 hours and, thereafter, concentrated *in vacuo*. The oily residue (1 g.) thus obtained was applied to preparative tlc plates. Elution with 40:2:1 (chloroform:ethanol:acetic acid) resulted in the separation of two major products: the faster-moving band gave 0.38 g. of V (35%), m.p. 135-136° (ethyl acetate:petroleum ether); ms: m/e (%): 246 (7)M⁺, 229 (14), 167 (43), 151 (31), 150 (51), 124 (24), 109 (80), 85 (18), 67 (100).

Anal. Calcd. for C₈H₁₀N₂O₅S: C, 39.02; H, 4.09; N, 11.38; S, 12.98. Found: C, 39.16; H, 4.09; N, 11.32; S, 12.86.

The slower-moving band gave 0.1 g. (15%) of 5-methyl-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide, identical in all respects with an authentic sample (6).

N-[*N'*-(Tetrahydropyran-2-yl)sulfamoyl]-2,6-dimethyl-4-pyrone-3-carboxamide (VI).

According to the procedure described for V, 0.75 g. (0.004 mole) of *N*-(tetrahydropyran-2-yl)sulfamide (II) were allowed to react with 0.67 g. (0.008 mole) of diketene, with the only difference, that at the end, the reaction mixture had to be refluxed for 15 minutes. Preparative tlc, in the same conditions as in V, yielded two major products: the faster-moving band gave 0.5 g. of VI (35%), m.p. 126-127° (ethyl acetate:petroleum ether); ¹H nmr (DMSO-d₆, δ): 8.72 (d, 1H, NH, J_{2-NH} = 9.5 Hz).

Anal. Calcd. for C₁₃H₁₈N₂O₆S: C, 47.27; H, 5.49; N, 8.48; S, 9.68. Found: C, 47.52; H, 5.37; N, 8.26; S, 9.39.

The slower-moving band gave 0.2 g. (18%) of a compound identical in all respects to V.

N-[*N'*-(2,3,4,6-Tetra-*O*-acetyl-β-*D*-glucopyranosyl)sulfamoyl]-2,6-dimethyl-4-pyrone-3-carboxamide (VII).

N-(2,3,4,6-Tetra-*O*-acetyl-β-*D*-glucopyranosyl)sulfamide (III), 2.0 g. (0.004 mole) were made to react with 0.67 g. (0.008 mole) of diketene, in the conditions described for V. The residue obtained, at the end, was a mixture of products, one of which was insoluble in ethyl acetate. Recrystallization from chloroform:ethanol yielded 0.46 g. of pure VII (20%), m.p. 179-180°; [α]_D = +98° (c, 0.05, chloroform).

Anal. Calcd. for C₂₂H₂₈N₂O₁₄S: C, 45.83; H, 4.86; N, 4.86. Found: C, 45.46; H, 5.00; N, 5.14.

Acknowledgments.

We are indebted to Professor Dr. Ramón Madroñero for his interest and encouragement.

REFERENCES AND NOTES

- (1) Part II. J. Diez, G. García-Muñoz, R. Madroñero and M. Stud, *J. Heterocyclic Chem.*, **10**, 469 (1973).
- (2) G. García-Muñoz, C. Ochoa, M. Stud and W. Pfleiderer, *ibid.*, **13**, 793 (1976); P. Goya and M. Stud, submitted.
- (3) G. García-Muñoz, R. Madroñero and M. Stud, *J. Heterocyclic Chem.*, **11**, 281 (1974); P. Goya and M. Stud, in preparation.
- (4) H. H. Hatt and C. K. Triffet, *Aust. J. Chem.*, **18**, 2045 (1965).
- (5) N. Yamaoka, K. Aso and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965); N. Yamaoka, B. A. Otter and J. J. Fox, *J. Med. Chem.*, **11**, 55 (1968).
- (6) R. Die, J. Diez, G. García-Muñoz, R. Madroñero and M. Stud, *J. Heterocyclic Chem.*, **9**, 973 (1972).
- (7) T. Kato, *Acc. Chem. Res.*, **7**, 265 (1974).
- (8) T. Kato, H. Yamanaka, N. Katagiri and S. Masuda, *Chem. Pharm. Bull.*, **20**, 133 (1972).
- (9) E. R. Reckondo and H. Rinderknecht, *Helv. Chim. Acta*, **42**, 1171 (1959).