ALTERNATIVE SYNTHESIS OF 4-METHYL-2*H*-1,2,6-THIADIAZIN-3(6*H*)-ONE 1,1-DIOXIDE, A STRUCTURAL ANALOGUE OF THYMINE

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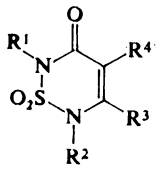
N-Alkylsulfamides react with methyl 3-methoxy-2-methyl-2-propenoate (*XI*) in aqueous hydrochloric acid under formation of methyl 3-(N'-alkylsulfamido)-2-methyl-2-propenoates (*VIIa* to *VIIc*). Attempted base-catalyzed cyclization of the ester *VIIb* was unsuccessful. The 2-benzyl derivative *IV* and the 6-benzyl derivative *V* were prepared by reaction of iodotrimethylsilane with the acid *VIII* and the amide *IX*, respectively. Hydrogenolytic removal of the benzyl groups in the 2- and 6-benzyl derivatives *IV* and *V* afforded the title compound *III*.

Replacement if carbonyl group by an SO_2 group represents one of structural modifications used in the series of pyrimidine[1-6] or purine bases[7-11] and their N-glycosyl derivatives[12,13]. A great number of known analogues of this type may be found among 2*H*-1,2,6-triadiazine 1,1-dioxides[3-6] and their derivatives with annelated five-membered heterocyclic rings[9-11]. Our interest in thiadiazine derivatives was aroused particularly by studies[14,15] of biological activity of compounds containing the NH—SO_2—NH grouping as a part of the heterocyclic ring.

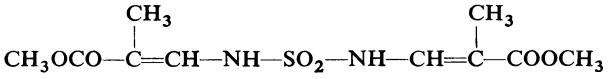
The hitherto described synthetic approaches to 4- and 5-substituted derivatives of 2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxide (*I*) are only of limited applicability. The 5-methyl derivative *II* was prepared[3] by reaction of diketene with sulfamide. Esters of 2-substituted 3-ethoxy-2-propenoic acids were used as starting compounds for the preparation of 4-substituted derivatives of the parent compound *I*; however, the first synthetic step, *i.e.* the reaction with sulfamide, takes place only with esters containing electronegative substituents[4] such as $CO_2C_2H_5$, CN or NO_2. The 4-methyl derivative *III* was synthesized from 4-methyl-5-isoxazolylsulfamide[5], obtained by treatment of 4-methyl-5-aminoisoxazole with sulfamyl chloride in 13% yield. In the present paper we describe the alternative synthesis of the compound *III* and its 2- and 6-benzyl derivatives *IV* and *V*, starting from the easily accessible methyl 3-methoxy-2-methyl-2-propenoate (*XI*).

Recently, we described the preparation of methyl 3-(N'-alkylureido)-2-methyl-2-propenoates as intermediates in the synthesis of 3-alkylthymines[16]. Because of the similar chemical behaviour of urea and sulfamide[17] it seemed interesting to apply the mentioned method to the synthesis of the analogous methyl 3-(N'-alkylsulfamido)-

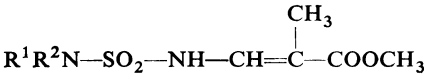
-2-methyl-2-propenoates. Goya and Stud[4] tried to obtain the compound *I* in a similar way by reaction of ethyl 3,3-diethoxypropanoate with sulfamide in dilute hydrochloric acid; however, they isolated 3,7-bis(ethoxycarbonylmethyl)perhydro-1,5,2,4,6,8--dithiatetrazocine 1,1,5,5-tetroxide as the sole product. (For the use of sulfamide in the synthesis of heterocyclic compounds see ref.[18].) By reaction of the ester *XI* with sulfamide in aqueous hydrochloric acid we obtained low yields of N,N'-bis-(2-methoxycarbonyl-1-propen-1-yl)sulfamide (*VI*) whose structure corresponded to



I; $R^1 = R^2 = R^3 = R^4 = H$
II; $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$
III; $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$
IV; $R^1 = CH_2C_6H_5$, $R^2 = R^3 = H$, $R^4 = CH_3$
V; $R^1 = R^3 = H$, $R^2 = CH_2C_6H_5$, $R^4 = CH_3$

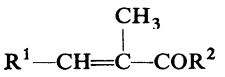


VI



(E, Z)

VIIa; $R^1 = H$, $R^2 = CH_3$
VIIb; $R^1 = H$, $R^2 = CH_2C_6H_5$
VIIc; $R^1 = R^2 = CH_3$



VIII; $R^1 = NHSO_2NHCH_2C_6H_5$, $R^2 = OH$
IX; $R^1 = OCH_3$, $R^2 = NHSO_2NHCH_2C_6H_5$
X; $R^1 = R^2 = NHSO_2NHCH_2C_6H_5$
XI; $R^1 = R^2 = OCH_3$
XII; $R^1 = OCH_3$, $R^2 = OH$
XIII; $R^1 = OCH_3$, $R^2 = Cl$

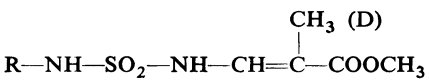
the previously described[16] ureylene derivative, prepared by reaction of the ester *XI* with urea. Under the above-mentioned conditions N-methyl and N-benzylsulfamide reacted with the ester *XI* to give mixtures of the corresponding methyl (*E*)- and (*Z*)-3-(N'-alkylsulfamido)-2-methyl-2-propenoates *VIIa* and *VIIb*, respectively. Reaction of N,N-dimethylsufamide with the ester *XI* afforded methyl (*E*)-3-(N',N'--dimethylsulfamido)-2-methyl-2-propenoate (*VIIc*) as the sole isomer. The stereo-

isomer (*Z*)-*VIIc* was prepared by photoisomerization of (*E*)-*VIIc*. To study the stability of the sulfamide derivatives *VII* towards hydrolysis we measured the kinetics of decomposition of *VIIb* in 0·1M-HCl at 25°C. The respective half-lives for compounds (*Z*)-*VIIb* and (*E*)-*VIIb* were 114·5 min and 41 min. This result shows that in an acid medium the sulfamido derivatives are less stable than the corresponding ureido derivatives[16]. In order to prevent hydrolysis of the synthesized sulfamido derivatives we carried out the reaction of N-benzylsulfamide with the ester *XI* in an anhydrous medium, the necessary methyl 2-formylpropanoate being generated *in situ* from the ester *XI* by iodotrimethylsilane which cleaves ether bonds under mild conditions[19]. The yields of compounds *VIIb* as well as the *E*/*Z*-isomer ratio, were approximately the same as in the original procedure. The configuration at the C=C bond in compounds *VIIa* – *VIIc* was determined on the basis of chemical shifts of the vinyl proton and the „inner" NH group proton, similarly as in the case of methyl 3-(N'--alkylureido)-2-methyl-2-propenoates[16] (for ^{1}H NMR spectra see Tables I and II).

Attempts to cyclize (*E*)-*VIIb* and (*Z*)-*VIIb* with sodium methoxide in methanol were unsuccessful. At room temperature only *E*/*Z*-isomerization took place whereas at elevated temperatures (80°C) the disappearing absorption at 270 nm indicated

TABLE I

^{1}H NMR Spectral data of compounds *VIIa* – *VIIc*, measured in deuteriochloroform (tetramethylsilane as internal standard)



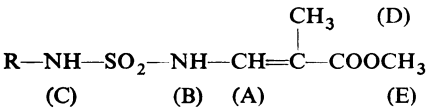
Compound	Chemical shifts δ, p.p.m.					Coupling constants Hz	
	$H_{(A)}$	$H_{(B)}$	$H_{(C)}$	$3H_{(D)}$	$3H_{(E)}$	J_{AB}	J_{AD}
E-*VIIa*[a]	7·43 dd	6·93 d	4·97 br s	1·76 d	3·73 s	12·0	1·0
Z-*VIIa*[b]	6·78 dd	9·88 br d	4·52 br s	1·78 d	3·73 s	11·0	1·5
E-*VIIb*[c]	7·30 s	6·70 br s	5·38 br t	1·58 d	3·68 s	—	1·0
Z-*VIIb*[d]	6·68 br d	9·80 br s	4·90 br t	1·72 d	3·72 s	10·0	1·0
E-*VIIc*[e]	7·46 d	7·08 d	—	1·77 s	3·70 s	12·0	—
Z-*VIIc*[f]	6·79 dd	—	—	1·77 d	3·73 s	11·0	1·0

[a] 2·74 (d, 3 H, CH_3; $J_{CH_3,NH}$ = 5·5 Hz), hexamethyldisiloxane as internal standard. [b] 2·72 (d, 3 H, CH_3, $J_{CH_3,NH}$ = 5·5 Hz). [c] 4·22 (d, 2 H, Ar—CH_2, $J_{CH_2,NH}$ = 6·0 Hz); 7·30 (s, 5 H_{arom}). [d] 4·21 (d, 2 H, Ar—CH_2, $J_{CH_2,NH}$ = 6·0 Hz); 7·28 (s, 5 H_{arom}). [e] 2·83 (s, 6 H, 2 CH_3). [f] 2·78 (s, 6 H, 2 CH_3).

decomposition of the starting compound. The inability of compounds *VIIb* to cyclize is apparently due to the lower nucleophilicity of the NH group caused by the electronegative SO_2 group. To compensate this unfavourable effect by increasing the reactivity of the electrophilic center of the carboxyl group, we prepared (*E*)-3-(N'--benzylsulfamido)-2-methyl-2-propenoic acid (*VIII*) by acid-catalyzed reaction of N-benzylsufamide and the acid *XII* in which the (*E*)-isomer was the principal product. Configuration of the acid *VIII* was confirmed by its conversion into the methyl ester (*E*)-*VIIb* by treatment with methanol in the presence of N,N'-dicyclohexylcarbodiimide. Reaction of *VIII* with diazomethane gave, instead of the desired methyl ester (*E*)-*VIIb*, a mixture of its N-methyl and N,N'-dimethyl derivatives. Treatment of the acid *VIII* with thionyl chloride in boiling dichloromethane, containing 0·1% dimethylformamide, afforded after several hours the desired cyclic proudct *IV* in 22% yield. Thus, the (*E*)-configuration of the starting acid does not hinder the cyclization reaction. By way of analogy with the isomerization of (*Z*)-methoxycarbonyl-2-propenoic acid[20] with thionyl chloride, we assume that also in the case of the acid *VIII* an *E*/*Z* isomerization takes place in the acyl halide stage. We increased the yield of the

TABLE II

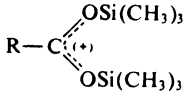
^{1}H NMR Spectral data of compounds *VIIa*–*VIIc*, measured in hexadeuteriodimethyl sulfoxide (hexamethyldisiloxane as internal standard)



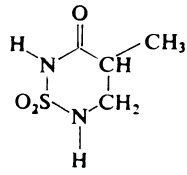
Compound	Chemical shifts δ, p.p.m.					Coupling constants Hz	
	$H_{(A)}$	$H_{(B)}$	$H_{(C)}$	3 $H_{(D)}$	3 $H_{(E)}$	J_{AB}	J_{AD}
E-*VIIa*[a,b]	7·33 s	10·05 s	7·50 d	1·75 s	3·67 s	—	—
Z-*VIIa*[c,b]	6·88 dd	9·70 d	7·50 d	1·75 d	3·70 s	12·0	1·0
E-*VIIb*[d]	7·26 s	9·98 s	8·14 t	1·60 s	3·56 s	—	—
Z-*VIIb*[e]	6·67 dd	9·53 d	8·18 t	1·60 d	3·59 s	12·0	1·0
E-*VIIc*[f]	7·28 d	10·30 s	—	1·68 d	3·56 s	—	1·5
Z-*VIIc*[g]	6·92 dd	9·83 d	—	1·68 d	3·63	11·0	1·5

[a] 2·53 (d, 3 H, CH_3NH; $J_{CH_3,NH}$ = 5·0 Hz), [b] Tetramethylsilane as internal standard; [c] 2·51 (d, 3 H, CH_3NH, $J_{CH_3,NH}$ = 5·0 Hz); [d] 4·02 (d, 2 H, Ar—CH_2; $J_{CH_2,NH}$ = 6·0 Hz); 7·26 (s, 5 H_{arom}); [e] 4·04 (d, 2 H, Ar—CH_2; $J_{CH_2,NH}$ = 6·0 Hz); 4·23 (s, 5 H_{arom}); [f] 2·63 (s, 6 H, 2 CH_3). [g] 2·66 (s, 6 H, 2 CH_3).

cyclic product *IV* using iodotrimethylsilane as cyclization reagent and working in dichloromethane at room temperature. Iodotrimethylsilane acts probably as a silylation reagent[21] transforming the acid *VIII* into the trimethylsilyl ester. Attack by another iodotrimethylsilane molecule can lead to the symmetrical ion *XIV* with a stabilized positive charge. An analogous cation is supposed in the cleavage of carboxylic acid esters with iodotrimethylsilane[22]. (For iodotrimethylsilane reactions see the reviews[23,24].) The ion *XIV* may react with the NH group either directly or after subsequent conversion into the acyl iodide (the formation of acyl iodides on prolonged treatment of carboxylic acid esters with iodotrimethylsilane has been proved[22]). We did not remove the traces of free iodine occuring during the reaction, since, according to Benkeser and coworkers[25], free iodine increases the reactivity of iodotrimethylsilane in the cleavage of carboxylic acid esters, forming a complex of the reagent with iodine. The iodine present catalyzes also the *E*/*Z*-isomerization as we found for the ester (*E*)-*VIIb*.



XIV



XV

The 6-benzyl derivative *V* was prepared by reaction of iodotrimethylsilane with N-benzyl-N′-(3-methoxy-2-methyl-2-propenoyl)sulfamide (*IX*) in dichloromethane at room temperature. We prepared the starting amide *IX* by reaction of N-benzylsulfamide with 3-methoxy-2-methyl-2-propenoyl chloride (*XIII*) in benzene in the presence of 2,4,6-trimethylpyridine as a proton acceptor. In the absence of the base the reaction afforded, in addition of the desired amide *IX*, the cyclic product *V* and N-benzyl-N′-[3-(N′-benzylsulfamido)-2-methyl-2-propenoyl]sulfamide (*X*). Obviously, in the course of the acylation the hydrogen chloride present removes the methoxy group and the arising formyl derivative cyclizes to the compound *V* or reacts with the sulfamide derivative to give the compound *X*.

Removal of the benzyl group in the thiazine derivatives *IV* and *V* by hydrogenolysis over palladium afforded the 4-methyl derivative *III*, whose physical properties were identical with those of the product prepared by the American authors[5]. Prolonged hydrogenolysis times led to hydrogenation of the double bond under formation of 4,5-dihydro-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxide (*XV*).

Compound *III* did not inhibit the growth of *Escherichia coli* B. at concentration 100 μg/ml.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 25°C/6·5 Pa for 8 h. ^{1}H NMR spectra were obtained with a Tesla 467 instrument (60 MHz) using tetramethylsilane as internal standard (unless stated otherwise); chemical shifts δ are given in ppm. UV spectra were taken on a Specord UV VIS spectrometer, IR spectra on a UR 10 instrument (both Carl Zeiss, Jena). Mass spectra were obtained with an AEI MS 902 double focus instrument (Associated Electric Industries, Manchester). Thin-layer chromatography was performed on Silufol UV_{254} sheets (Kavalier, Votice, Czechoslovakia), preparative HPLC chromatography was run on an instrument made in the workshops of the Institute (0·8 × 25 cm column filled with silica gel or a 1·3 × 25 cm column with Separon SI C_{18} (8 μm)) equipped with a variable wavelength UV detector (Developmental Workshops of Czechoslovak Academy of Sciences, Prague).

Starting Compounds

Methyl 3-methoxy-2-methyl-2-propenoate[26], sulfamide[27], N-methylsulfamide[28] and N,N-dimethylsulfamide[29] were prepared by the described procedures. N-Benzylsulfamide (m.p. 106°C, reported[30] mp. 106—107°C) was prepared in 80% yield by reaction of sulfamide with benzylamine under conditions described by Paquin[17] for preparation of N-butylsulfamide. Iodotrimethylsilane was synthesized according to Schmidt and Russ[31] and was stored over copper powder.

N,N'-Bis(2-methoxycarbonyl-1-propen-1-yl)sulfamide (*VI*)

The ester *XI* (0·65 g; 5 mmol) was added to a stirred solution of sulfamide (0·48 g; 5 mmol) in 5M-HCl (3·75 ml). After stirring at room temperature for 1 h, homogeneous mixture was diluted with water (3·75 ml) and extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with saturated sodium hydrogen carbonate solution (3 × 20 ml), dried over sodium sulfate and taken down *in vacuo*. Crystallization of the residue from ethyl acetate gave 54 mg (4%) of the compound *VI*, melting at 157°C; UV spectrum (50% aqueous ethanol): λ_{max} 254 nm (log ε 4·23); ethanol — 0·1M-NaOH 1 : 1): λ_{max} 286 nm and 322 nm (log ε 4·55 and 4·47, respectively). For $C_{10}H_{16}N_2O_6S$ (292·3) calculated: 41·09% C, 5·52% H, 9·58% N, 10·96% S; found: 40·71% C, 5·55% H, 9·59% N, 11·26% S.

Methyl 3-(N'-Alkylsulfamido)-2-methyl-2-propenoates *VIIa*—*VIIc*

The ester *XI* (0·52 g; 4 mmol) was added to a stirred suspension of N-alkylsulfamide (4 mmol) in 5M-HCl (3 ml). After stirring at room temperature for 30 min, the mixture was diluted with water (3 ml) and worked up as described for the compound *VI*. The sirupy mixtures of the (*Z*)- and (*E*)-isomers were separated on a column of silica gel (100 g; 30—60 μm) in benzene–ethyl acetate (3 : 1 for *VIIa* and *VIIc* and 5 : 1 for *VIIb*). The yields, elemental analyses and spectral data are given in Tables I—IV.

Methyl 3-(N'-Benzylsulfamido)-2-methyl-2-propenoate (*VIIb*) (Alternative Synthesis)

A mixture of N-benzylsulfamide (0·247 g; 1·33 mmol), the ester *XI* (0·173 g; 1·33 mmol), iodotrimethylsilane (0·5 ml; 3·51 mmol) and dichloromethane (6 ml) was stirred at room temperature for 24 h, diluted with the ethyl acetate (150 ml), washed with 5% sodium sulfite solution (3 × 10 ml), dried and taken down. HPLC of the residue on a silica gel column in dichloromethane–ethyl acetate (4 : 1) afforded (*Z*)-*VIIb* (79 mg; 21%), (*E*)-*VIIb* (152 mg; 40%) and the unreacted N-ben-

zylsulfamide (93 mg; 37·5%). The products were identical (melting points, IR spectra and HPLC elution times on reversed phase in methanol–water 7 : 3) with the compounds (*Z*)- and (*E*)-*VIIb*, obtained in the preceding experiment.

TABLE III

Yields, melting points and elemental analyses of (*Z*)- and (*E*)-isomers of compounds *VIIa*—*VIIc*

Compound	Yield %	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% S
Z-VIIa	11·0	88[a] (ether)	$C_6H_{12}N_2O_4S$ (208·2)	34·60 34·94	5·81 5·82	13·45 13·39	15·40 15·05
E-VIIa	37·4	80—81 (ether–light petroleum)		35·05	5·79	13·59	14·95
Z-VIIb	28·1	104 (toluene)	$C_{12}H_{16}N_2O_4S$ (284·4)	50·69 50·44	5·67 5·60	9·85 10·00	11·28 11·37
E-VIIb	49·7	119 (toluene)		50·69	5·63	9·40	11·13
E-VIIc	52·7	105 (toluene)	$C_7H_{14}N_2O_4S$ (222·3)	37·82 37·92	6·35 6·38	12·60 13·06	14·43 14·16
Z-VIIc	43·0[a]	49[b]		38·14	6·48	12·82	14·25

[a] Yield of compound obtained by photoisomerization; [b] m.p. of residue after evaporation of chromatographic fraction.

TABLE IV

UV Spectral data of compounds *VIIa*—*VIIc* (λ_{max} values in nm)

Compound	ethanol–water (1 : 1)		ethanol–0·1M-NaOH (1 : 1)	
	λ_{max}	log ε	λ_{max}	log ε
Z-VIIa	264	4·04	292	4·32
E-VIIa	256	3·98	290	4·24
Z-VIIb	259	4·06	292	4·40
E-VIIb	257	4·21	292	4·41
Z-VIIc	265	4·11	296	4·29
E-VIIc	256	4·20	290	4·45

Methyl (*Z*)-3-(N′,N′-Dimethylsulfamido)-2-methyl-2-propenoate ((*Z*)-*VIIc*)

A solution of (*E*)-*VIIc* (120 mg) in methanol (120 ml) was irradiated under nitrogen with a 150 W high-pressure mercury lamp at 25°C for 30 min in a quartz apparatus equipped with a 20% aqueous dimethylformamide filter. The mixture was taken down and the residue chromatographed (HPLC) on a silica gel column, affording 56 mg (47%) of teh starting (*E*)-*VIIc* and 52 mg (43%) of the desired (*Z*)-isomer, m.p. 49°C. Mass spectrum: *m/z* 222 M^+, 191 $(M—CH_3)^+$, 124 $(M—CH_3 . OH)^+$. For elemental analysis and spectral data see Tables I—IV.

(*E*)-3-(N′-Benzylsulfamido)-2-methyl-2-propenoic Acid (*VIII*)

A) To a solution of the acid *XII* (1·16 g; 10 mmol) and N-benzylsulfamide (1·85 g; 10 mmol) dioxane (10 ml) 35% hydrochloric acid (5 ml) was added. After standing at room temperature for 30 min, the mixture was diluted with water (10 ml) and allowed to stand at 0°C for 6 h. The crystalline product *VIII* was filtered, washed with ice-cold water, dried over potassium hydroxide overnight and crystallized from acetone–light petroleum, affording 1·22 g (45·2%) of compound *VIII*, m.p. 145°C. UV spectrum (50% aqueous ethanol): λ_{max} 254 nm (log ε 4·13); (ethanol –0·1 M-NaOH 1 : 1): λ_{max} 274 nm (log ε 4·17). ^{1}NMR spectrum (hexadeuteriodimethyl sulfoxide: 1·64 (s, 3 H, CH_3); 4·07 (d, 2 H, CH_2-Ar, J_{CH_2NH} = 6·0 Hz); 7·30 (s, 6 H, —CH= and H_{arom}); 8·15 (t, 1 H, HN—CH_2—Ar, J_{NH,CH_3} = 6·3 Hz); 9·97 (br s, 1 H, HN—CH). For $C_{11}H_{14}N_2O_4S$ (270·3) calculated: 48·88% C, 5·22% H, 10·36% N, 11·86% S; found: 48·45% C, 5·18% H, 10·64% N, 11·69% S.

B) A mixture of the acid *XII* (0·116 g; 1 mmol), N-benzylsulfamide (0·186 g; 1 mmol), iodotrimethylsilane (0·5 ml; 3·5 mmol) and dichloromethane (5 ml) was stirred at room temperature for 20 h, dilute with ehtyl acetate (100 ml), washed with 5% sodium sulfite solution (3 × 10 ml), dried over sodium sulfate and taken down. Crystallization of the residue from acetone–light petroleum afforded 0·15 g (55·5%) of the product, melting at 145°C without depression on admixture of the acid *VIII* prepared by the procedure *A*. Both samples aad identical retention time sin reversed phase HPLC in methanol–water (7 : 3). Mother liquors from crystallization of the acid *VIII* were chromatographed on a column (0·8 × 50 cm) of silica gel (Separon SI VSK; 10 μm) in dichloromethane, giving further 25 mg (8·8%) of the acid *VIII*.

Methylation of the Acid *VIII*

A) A mixture of the acid *VIII* (135 mg; 0·5 mmol), N,N′-dicyclohexylcarbodiimide (206 mg; 1 mmol) and methanol (10 ml) was set aside at room temperature for 5 h. The reaction was monitored by thin-layer chromatography in toluene–ethyl acetate (2 : 1). After evaporation of the solvent *in vacuo*, the residue was chromatographed on a column of silica gel in the above-mentioned system. Crystallization of the main fraction from toluene afforded 45 mg of the pure compound (*E*)-*VIIb*. The first fraction gave 5 mg of crystals whose chromatographic mobility corresponded to that of (*Z*)-*VII*b.

B) An ethereal solution of diazomethane was added to a stirred solution of the compound *VIII* (27 mg) in methanol (1 ml) until a faintly yellow colouration persisted. After adding a drop of acetic acid, the mixture was taken down *in vacuo* and the residue was codistilled with toluene. The crystalline residue (29 mg) consisted of two compounds of molecular peaks *m/z* 298 and 312, corresponding to N-methyl and N,N′-dimethyl derivatives of *VIIb*.

2-Benzyl-4-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-Dioxide (*IV*)

A) A mixture of the acid *VIII* (0·400 g; 1·48 mmol), iodotrimethylsilane (2 ml) and dichloromethane (20 ml) was stirred at room temperature until the acid dissolved (about 48 h), diluted with ethyl acetate (20 ml), washed with 5% sodium sulfite solution (2 × 20 ml), dried over sodium sulfate and taken down. The residue was crystallized from ethyl acetate–n-heptane (1 : 10), yielding 0·244 g (61%) of the product, m.p. 162°C. UV spectrum (ethanol — 0·1M-HCl, 1 : 1): λ_{max} 266 nm (log ε 3·84); (ethanol — 0·1M-NaOH, 1 : 1): λ_{max} 303 nm (log ε 3·95). ^{1}H NMR spectrum (deuteriochloroform): 1·88 (d, 3 H, CH_3, $J_{CH3,5}$ = 1·5 Hz); 4·94 (s, 2 H, CH_2-Ar); 6·79 (d, 1 H, $H_{(5)}$, J_{5,CH_3} = 1·5 Hz); 7·35 (s, 5 H, H_{arom}). Mass spectrum: *m/z* 252 M^+, 188 $(M—SO_2)^+$, 187 $(M—HSO_2)^+$, 111 $(188 - C_6H_5)^+$. For $C_{11}H_{12}N_2O_3S$ (252·3) calculated: 52·36% C, 4·79% H, 11·11% N, 12·71% S; found: 52·02% C, 4·71% H, 11·03% N, 12·84% S.

B) Thionyl chloride (2 ml), followed by dimethylformamide (0·02 ml) was added to a stirred suspension of the acid *VIII* (0·860 g; 3·18 mmol) in dichloromethane (25 ml) and the mixture was refluxed for 6 h. After standing at room temperature for 12 h, dichloromethane and thionyl chloride were removed *in vacuo*. The residue was dissolved in ethyl acetate (50 ml), the solution washed with water, sodium hydrogen carbonate solution, dried over sodium sulfate and taken down. The residue was chromatographed on a column of silica gel (50 g, 30—60 μm) in ligroin–ethyl acetate (1 : 1), containing 0·5% of acetic acid. On addition of toluene–light petroleum, the chromatographic fraction crystallized, affording 174 mg (21·7%) of compound *IV*, m.p. 159—160°C, which after recrystallization from ethyl acetate–n-heptane (1 : 10) melted at 162 to 163°C without depression on admixture with *IV*, prepared by the procedure *A*.

E/*Z*-Isomerization of the Ester (*E*)-*VIIb* with Iodine

The ester (*E*)-*VIIb* (1 mg; 3·4 . 10^{-3} mmol) was added to a stirred solution of iodine in dichloromethane (4 ml; 1·6 . 10^{-3} mol l^{-1}). After 1 h, the mixture was diluted with dichloromethane (10 ml), washed with 5% sodium sulfate solution (2 × 3 ml), dried over sodium sulfate and taken down. According to reversed-phase HPLC in methanol–water (7 : 3), the residue was a mixture of (*E*)-*VIIb* and (*Z*)-*VIIb* in the ratio 1·44 : 1·00.

(*E*)-N-Benzyl-N′-(3-methoxy-2-methyl-2-propenoyl)sulfamide (*IX*)

A) A stirred mixture of N-benzylsulfamide (1·85 g; 10 mmol), chloride *XIII* (1·16 g; 10 mmol), 2,4,6-trimethylpyridine (1·21 g; 10 mmol) and benzene (20 ml) was heated to 70°C for 6 h, cooled, washed with water (2 × 10 ml), dried over sodium sulfate and taken down. The sirupy residue on trituration with ether afforded 0·82 g of the crude amide *IX* which was crystallized from ethanol, giving 0·634 g (22·3%) of pure (*E*)-*IX*, m.p. 159—161°C. UV spectrum (50% aqueous ethanol): λ_{max} 255 nm (log ε 4·11); (ethanol–0·1M-NaO : λ_{max} 255 nm (log ε 4·10). ^{1}H NMR spectrum (deuteriochloroform with 10% hexadeuteriodimethyl sulfoxide): 1·66 (s, 3 H, CH_3, $J_{CH3,2}$ = 1 Hz); 3·80 (s, 3 H, CH_3O); 4·13 (d, 2 H, CH_2—Ar, $J_{CH_2,NH}$ = 6·0 Hz); 6·68 (t, 1 H, CH_2—NH, J_{NH,CH_2} = 6·0 Hz); 7·30 (s, 6 H, 5 H_{arom} and CH=); 10·46 (br s, 1 H, SO_2NHCO). For $C_{12}H_{16}N_2O_4S$ (284·3) calculated: 50·69% C, 5·67% H, 9·85% N, 11·28% S; found: 50·92% C, 5·66% H, 10·01% N, 11·40% S.

B) A stirred mixture of N-benzylsulfamide (3·70 g; 19·9 mmol), chloride *XIII* (3·18 g; 23·6 mmol) and benzene (55 ml) was refluxed for 12 h. N-Benzylsulfamide dissolved during 1 h and the product (1.094 g; 25%) separated from the boiling mixture. The mixture was filtered while hot, and the product was washed with benzene. Crystallization from ethanol gave 0·576 g (13%) of material melting at 177—179°C which was assigned the structure *X* according to elemental analysis and

UV and ^{1}H NMR spectra. UV spectrum (ethanol–water 1 : 1): λ_{max} 265 nm (log ε 4·09); (ethanol–0·1M-NaOH 1 : 1): λ_{max} 298 nm (log ε 4·27). ^{1}H NMR spectrum, hexamethyldisiloxane as internal standard (hexadeuteriodimethyl sulfoxide): 1·63 (s, 3 H, CH_3), 4·09 (d, 4 H, CH_2—Ar, $J_{CH_2,NH}$ = = 6·0 Hz); 7·29 (s, 1 H, CH=); 7·29 (d, 10 H, H_{arom}); 7·96 (t, 1 H, CH_2—NH, J_{NH,CH_2} = 6·0 Hz); 8.01 (t, 1 H, CH_2—NH, J_{NH,CH_2} = 6·0 Hz); 10·02 (br s, 1 H, NH—CH=); exchange in deuterium oxide: 1·57 (s, 3 H, CH_3); 4·10 (s, 4 H, CH_2—Ar); 7·16 (s, 1 H, CH=), 7·30 (s, 10 H, H_{arom}). For $C_{18}H_{22}N_4O_5S_2$ (438·5) calculated: 49·30% C, 5·06% H, 12·78% N, 14·62% S; found: 49·61% C, 5·05% H, 12·93% N, 12·93% N, 14·36% S.

Mother liquors from crystallization of *X* were concentrated and the separated compound *IX* (1·028 g; 18·2%) was crystallized from ethanol to give 0·86 g (15%) of a crystalline mixture of (*E*)- and (*Z*)-*IX* in the ratio 3 : 2; m.p. 154°C. The isomer ratio was determined by integration of the vinylic proton signals after exchange in deuterium oxide. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide) (*E*)-isomer *IX*: 1·52 (s, 3 H, CH_3); 3·76 (s, 3 H, CH_3O); 4·12 (d, CH_2—Ar, $J_{CH_2,NH}$ = 6·0 Hz), 7·28 (s, 6 H, CH= and 5 H_{arom}); 7·99 (t, 1 H, CH_2—NH, J_{NH,CH_2} = 6·0 Hz); 10·77 (s, 1 H, NH—CH=); exchange in deuterium oxide: 1·54 (s, 3 H, CH_3); 3·79 (s, 3 H, CH_3O); 4·12 (s, 2 H, CH_2—NH); 7·15 (s, 1 H, CH=); 7·28 (s, 5 H, H_{arom}). (*Z*)-Isomer: *IX*: 1·52 (s,3 H, CH_3); 3·80 (s, 3 H, CH_3O);4·15 (d, 2 H, CH_2-Ar, $J_{CH_2,NH}$ = 6·0 Hz); 6·81 (s, 1 H, CH=); 7·28 (s, 5 H, H_{arom}); 8·28 (t, 1 H, CH_2—NH, J_{NH,CH_2} = 6·0 Hz); 9·58 (s, 1 H, NH—CH=); exchange in deuterium oxide: 1·54 (s, 3 H, CH_3); 3·80 (s, 3H, CH_3O); 4·16 (s, 2 H, CH_2—NH); 6·78 (s, 1 H, CH=); 7·28 (s, 5 H, H_{arom}).

The combined mother liquors were concentrated and extracted with ether (3 × 80 ml). After evaporation of the ether, the residue was chromatographed on a silica gel column in toluene–ethyl acetate (2 : 1), affording 1·503 g of crystalline material which on crystallization from toluene melted at 125°C, without depression on admixture with an authentic sample of *V*.

6-Benzyl-4-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-Dioxide (*V*)

A mixture of the amide *IX* (145 mg; 0·52 mmol), iodotrimethylsilane (0·25 ml; 1·76 mmol) and dichloromethane (3 ml) was stirred at room temperature for 24 h. After dilution with ethyl acetate (100 ml), the mixture was worked up as described for the compound *IV*. Crystallization of the residue from toluene afforded 92 mg (73%) of compound *V*, m.p. 125°C. UV spectrum (ethanol–0·1M-HCl, 1 : 1) λ_{max} 302 nm (log ε 3·81); (ethanol–0·1M-NaOH, 1 : 1): λ_{max} 284 nm (log ε 3·91). IR spectrum (chloroform), cm^{-1}: 3 355 (NH): 1 694 sh, 1 649 (C=O, C=C), 1 540 (C=O, amid II); 1 332, 1 167 (SO_2). ^{1}H NMR spectrum (deuteriochloroform): 1·84 (d, 3 H, CH_3, $J_{CH_3,5}$ = 1·0 Hz); 4·85 (s, 2 H, CH_2-Ar); 6·79 (d, 1 H, $H_{(5)}$, J_{5,CH_3} = 1·0 Hz); 7·37 (s, 5 H, H_{arom}); 8·40 (s, 1 H, $H_{(2)}$). Mass spectrum: *m/z* 252 M^+, 188 $(M - SO_2)^+$, 172 $(M - SO_2NH_2)^+$, 144, 115, 91 $(C_6H_5CH_2)^+$, 65 $(91 - C_2H_2)^+$. For $C_{11}H_{12}N_2O_3S$ (252·3) calculated: 52·36% C, 4·79% H, 11·11% N, 12·71% S; found: 52·71% C, 4·66% H, 10·68% N, 12·68% S.

4-Methyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-Dioxide (*III*)

A) Compound *V* (278 mg; 1·5 mmol) in ethanol (25 ml) was hydrogenated at ordinary pressure at room temperature over palladium on charcoal (5%, 380 mg) in an apparatus equipped with a septum for sample withdrawal. (The catalyst was prepared by evaporation of an aqueous solution of palladium chloride with charcoal.) Hydrogenolysis of the benzyl group was monitored by reversed phase HPLC in methanol–0·2% acetic acid (2 : 3). After the end of hydrogenation (about 1 h) the apparatus was evacuated, flushed with nitrogen, the catalyst was filtered and the filtrate taken down *in vacuo*. HPLC in dichloromethane–ethyl acetate–acetic acid (60 : 10 : 1) afforded 201 mg (82·6%) of chromatographically pure compound *III* which was crystallized from an ethyl

acetate–toluene–light petroleum mixture to give 132 mg (54·3%) of *III*, m.p. 154–159°C; UV spectrum (ethanol–0·1M-HCl): λ_{max} 283 nm (log ε 3·65), (ethanol–0·1M-NaOH, 1 : 1); λ_{max} 304 nm (log ε 3·88). ^{1}H NMR spectrum (deuteriochloroform — hexadeuteriodimethyl sulfoxide): 1·82 (d, 3 H, CH_3, $J_{CH_3,5}$ = 1·0 Hz); 6·93 (d, 1 H, J_{5,CH_3} = 1·0 Hz); 11·77 (br s, 2 H, $H_{(2)}$ and $H_{(6)}$). IR spectrum (KBr), cm^{-1}: 3 215 (NH): 1 659 sh, 1 645 (C=O), 1 525 (C=C), 1 390 (CH_3); 1 345, 1 163, 576 (SO_2). Mass spectrum: *m/z* 162 M^+, 119, 98, 83, 82, 71, 55. For $C_4H_6N_2O_3S$ (162·2) calculated: 29·62% C, 3·73% H, 17·28% N, 19·77% S; found: 30·05% C, 3·64% H, 17·31% N, 19·55% S.

B) Hydrogenation of compound *IV* (50 mg; 0·2 mmol) in ethanol (5 ml) over palladium catalyst (50 mg) under the conditions given in the preparation A afforded 27 mg (83·2%) of the chromatographically pure product *III*, which was crystallized (*vide supra*) to give 17 mg (52·5%) of *III*, m.p. 154–158°C; no m.p. depression with the sample prepared by hydrogenolysis of compound *V*.

4,5-Dihydro-4-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-Dioxide (*XV*)

The compound *IV* (189 mg) was hydrogenated in ethanol (10 ml) over palladium on charcoal (5%, 200 mg) at ordinary pressure and room temperature for 12 h. The catalyst was filtered off, the filtrate taken down and the sirupy residue dissolved in ethyl acetate (100 ml). The solution was washed with water (3 × 10 ml), dried over sodium sulfate, taken down and the residue dissolved in ethanol, evaporated with silica gel (30–60 μm, 300 mg), applied on a column of silica gel (25 g) and eluted with a mixture of ethyl acetate, toluene and formic acid (25 : 25 : 1). Concentration of the eluate and codistillation of the residue with benzene (3 × 15 ml) afforded the crystalline product, m.p. 92°C, which did not absorb in the 250 nm region. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 1·08 (d, 3 H, CH_3, $J_{CH_3,H(4)}$ = 7·0 Hz); 3·36 (m, 3 H, CH—CH_2); 7·90 (br s, 1 H, $H_{(6)}$); 11·51 (br s, 1 H, $H_{(2)}$). IR spectrum (KBr), cm^{-1}: 3 215, 3 048 (NH); 1 707 (C=O); 1 439 (CH_2); 1 388 (CH_3); 1 334, 1 177, 571 (SO_2). Mass spectrum: *m/z* 164 M^+.

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