THE SYNTHESIS OF SUBSTITUTED 2*H*-1,2-BENZOTHIAZINES 1,1-DIOXIDES

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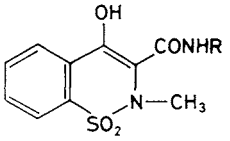
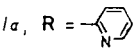
The base-catalyzed rearrangement of the esters of 2*H*-1,2-benzothiazolin-3-one-2-acetate 1,1-dioxide (*IIa*–*IIc*) afforded substituted 2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxides *IIIa*–*IIIc*. After N-alkylation and aminolysis the antiinflammatory drugs piroxicam and isoxicam were obtained.

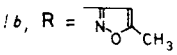
In our previous communication[1] we demonstrated that on alkylation of saccharin with chloroacetic acid esters under conditions of phase transfer catalysis esters of 1,1-dioxide of 2*H*-1,2-benzisothiazoline-3-one-2-acetate *IIa*–*IIc* may be prepared in high yields. In this paper we decided to investigate their conversion to alkyl esters of 2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide *IIIa*–*IIIc* which we further used for the preparation of highly effective antiinflammatory drugs[2,3] piroxicam (4-hydroxy-2-methyl-N-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, *Ia*) and isoxicam (4-hydroxy-2-methyl-N-(5-methyl-3-isoxazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, *Ib*).

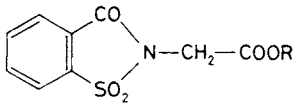
The main step in the construction of the benzothiazine skeleton of compounds *IIIa*–*IIIc* is the intramolecular Dieckmann condensation of esters *IIa*–*IIc* under basic conditions. These rearrangements have already been described in literature[4,5], but the results reported were not consistent. Therefore we decided to check the effect of the reaction conditions on the yields of the required derivatives *IIIa*–*IIIc*. As a model substance of the study of the rearrangement we chose methyl ester *IIa*. In the reaction catalysed with sodium methoxide in methanol we obtained, in agreement with literature[5], derivative *IIIa* in 70% yield, and, in addition, a small amount of N-methyl derivative *Va*. On prolongation of the reaction time the amount of compound *Va* in the product increased, while an excessive decrease of the required ester *IIIa* took place simultaneously. When the rearrangement was done in the presence of sodium methoxide in dimethyl sulfoxide we could not detect N-methyl derivative *Va* in the reaction mixture, it is true, but we could isolate ester *IIIa* only, in 25% yield. Further we demonstrated that in the reaction catalysed with dimsyl sodium in dimethyl sulfoxide only the benzothiazine derivative *IIIa* was formed in

a relatively good yield, 52% (see Table I). We consider that N-methyl derivative *Va* is formed during the rearrangement with sodium methoxide in methanol by a consecutive methylation reaction with methanol, as already observed[5].

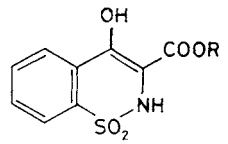


Ia, R = 

Ib, R = 



IIa, R = CH_3
IIb, R = $CH_2CH_2OCH_3$
IIc, R = $CH_2CH_2OC_2H_5$



IIIa, R = CH_3
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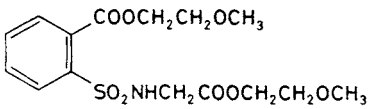
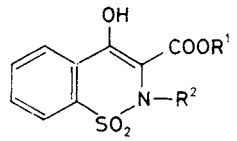
IIIc, R = $CH_2CH_2OC_2H_5$



IV



Va, $R^1 = R^2 = CH_3$
Vb, $R^1 = CH_3$; $R^2 = C_2H_5$
Vc, $R^1 = CH_2CH_2OCH_3$; $R^2 = CH_3$
Vd, $R^1 = CH_2CH_2OC_2H_5$; $R^2 = CH_3$

TABLE I

Conditions and the results of the rearrangements of esters *IIa*—*IIc*

Compound	Base	Product	Yield, %
IIb	$CH_3OCH_2CH_2ONa$	*IIIb*	88
	DMSO[a]	*IIIb*	55
	$(CH_3OCH_2CH_2O)_2Ca$	*IV*	84
IIc	$CH_3CH_2OCH_2CH_2ONa$	*IIIc*	68
	DMSO[a]	*IIIc*	52
IIa	$CH_3OCH_2CH_2ONa$	*IIIa*	25
		IIIb	51
	$CH_3CH_2OCH_2CH_2ONa$	*IIIa*	27
		IIIc	47

[a] A solution of dimsyl sodium in dimethyl sulfoxide.

On the basis of these observations we carried out the rearrangement of the esters *IIb* and *IIc* under catalysis with sodium alkoxides in corresponding alcohols, or by using dimsyl sodium in dimethyl sulfoxide. The results are summarized in Table I. The best results were obtained when corresponding alkoxyalkoxides in alkoxy-alcohol were used, while the reactions catalysed with dimsyl sodium in dimethyl sulfoxide gave relatively lower yields of compounds *IIIb* and *IIIc*.

In the reaction catalysed with calcium methoxyethoxide, generated from 2-methoxy-ethanol and calcium hydride only the cleavage of the benzisothiazoline ring took place and the intermediate *IV* was obtained in a high yield (84%). This could be cyclized to derivative *IIIb* under the effect of sodium 2-methoxyethoxide. From this finding we consider that the basicity of the calcium salt is unsufficient for the formation of the carbanion indispensable for the subsequent cyclization reaction.

From the point of view of the target products it is advantageous[6] if the work is carried out with alkoxyalkyl esters *IIIb* or *IIIc*. For these reasons we tried to carry out the rearrangement under simultaneous transesterification of the easily accessible methyl ester *IIa* with sodium 2-alkoxyalkoxide in alkoxy alcohol. In all instances we were able to isolate both esters *IIIa* and *IIIb*, or *IIIa* and *IIIc*, respectively, in good yields from the reaction mixture, in a 1 : 2 ratio (Table I). In agreement with the literature data[5] we confirmed on the basis of the presence of the signal at 11·25–11·50 ppm in the ^{1}H NMR spectrum, that the synthetized compounds *IIIb* and *IIIc* are stable in their enol form.

N-Alkylation of esters *IIIa* and *IIIb* with alkyl iodides in aqueous acetone took place slowly[7–9], and in relatively poor yields. We found that when the reaction was carried out under the conditions of phase transfer catalysis and in the presence of alkyl sulfates as alkylation reagent, the yields could be increased substantially. As phase transfer catalyst benzyltriethylammonium chloride was used, while as base sodium hydroxide was better than potassium carbonate (Table II).

TABLE II

Conditions and results of N-alkylation of esters *IIIa*–*IIIc*

Compound	$R^1_2SO_4$	Base	Product	Yield, %
IIIa	CH_3	NaOH	*Va*	68
	C_2H_5	NaOH	*Vb*	65
IIIb	CH_3	NaOH	*Vc*	65
		K_2CO_3	*Vc*	57
IIIc	CH_3	NaOH	*Vd*	63
		K_2CO_3	*Vd*	52

The 2-methoxyethyl- or 2-ethoxyethyl-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine--3-carboxylate 1,1-dioxides *Vc* or *Vd* were submitted to azeotropic aminolysis in xylene. Using 2-aminopyridine for this reaction we thus prepared piroxicam *Ia* in 97 and 92% yields, and from ester *Vc* and 3-amino-5-methylisoxazole isoxicam *Ib* was prepared in 86% yield. The structures of compounds *IIIa*–*IIIc*, *IV*, *Va*–*Vd*, and *Ia* and *Ib* were confirmed on the basis of their ^{1}H NMR spectra, infrared spectra and elemental analyses.

In comparison with the known procedures[6,9] the advantages of this synthesis consist primarily in the high yields of the intermediates *IIIb*, *IIIc*, *IVc* and *IVd*, *Ia* and *Ib*, further in their easy isolation and the short reaction times.

EXPERIMENTAL

The temperature data were not corrected. The melting points were determined on a Boetius block (C. Zeiss, Jena). The infrared spectra were measured on a Perkin–Elmer 325 (Bodenseewerk) instrument, the ^{1}H NMR spectra on a Varian XL-100-15 (Palo Alto) instrument, using tetramethylsilane as internal reference.

Chemicals: Esters *IIa* (m.p. 117–119°C), *IIb* (m.p. 91–92°C), and *IIc* (m.p. 48–49°C) were prepared according to ref.[1]. The solvents were dried according to ref.[10] and stored over molecular sieves.

Base-catalysed Rearrangements of Esters *IIa*–*IIc*

A. Catalysis with sodium 2-alkoxyalkoxides. *a*) Sodium (18·2 g; 0·79 gatom) was dissolved in a mixture of 2-methoxyethanol (198 ml) and toluene (8 ml) under stirring and nitrogen and ester *IIb* (59·2 g; 0·20 mol) was added in one portion to the solution at 120°C. The mixture was stirred for 15 min and poured onto a mixture of ice and hydrochloric acid (200 ml). The precipitated material was filtered off, washed with water and crystallized from toluene to afford 52·3 g (0·175 mol) of 2-methoxyethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide, m.p. 124–126·5°C (ref.[6] 120–122°C), yield 88%. IR spectrum (cm^{-1}, KBr): *ν* 3 430 m (OH), 1 658 s (CO), 1 381 s, 1 178 s (SO_2). ^{1}H NMR spectrum (*δ*, C^2HCl_3): 3·39 s (3 H, CH_3), 3·71 m (2 H, CH_2), 4·45 m (2 H, CH_2), 6·41 s (1 H, NH), 7·60–8·06 m (4 H, protons of the nucleus), 11·50 s (1 H, OH). – *b*) Analogously as under *a*), ester *IIIc* was prepared from ester *IIc* under the effect of sodium 2-ethoxyethoxide in 2-ethoxyethanol. M.p. 99–101°C (toluene), yield 68%. For $C_{13}H_{15}NO_6S$ (313·3) calculated: 49·83% C, 4·83% H, 4·47% N, 10·23% S; found: 49·69% C, 4·78% H, 4·32% N, 10·01% S. IR spectrum (cm^{-1}, $CHCl_3$): *ν* 3 450 w (OH), 1 670 s (CO), 1 375 s, 1 174 s (SO_2). ^{1}H NMR spectrum (*δ*, C^2HCl_3): 1·20 t (3 H, CH_3), 2·55 q (2 H, CH_2) *J* = 6·5 Hz, 3·73 m (2 H, CH_2), 4·45 m (2 H, CH_2), 6·26 s (1 H, NH), 7·60–8·08 (4 H, ring protons), 11·25 s (1 H, OH).

B. Catalysis with dimsyl sodium in dimethyl sulfoxide. *a*) Ester *IIa* (6·0 g, 20 mmol) was added at once to a solution of dimsyl sodium in dimethyl sulfoxide, prepared from 2·0 g (65 mmol) of sodium hydride (80% suspension in oil) and dimethyl sulfoxide (20 ml), and the mixture was stirred at 0°C for 30 min. After decomposition with icy water the precipitate formed was filtered off and washed with water. Crystallization from toluene gave 3·29 g (11 mmol) of ester *IIIa*, m.p. 125–126°C, in 55% yield. – *b*) Analogously as under *a*) ester *IIIc* was prepared from ester *IIc* on reaction with dimsyl sodium in dimethyl sulfoxide. M.p. of the product was 98–100°C, yield 52%.

C. Rearrangement of ester *IIa* with sodium 2-alkoxyalkoxides. *a*) Analogously as under A *a*) ester *IIa* (0·51 g, 2 mmol) was reacted with sodium (0·18 g, 8 mgatom) in 2-methoxyethanol (2·5 ml to give 0·44 g of a solid. Column chromatography (silica gel, chloroform–methanol as eluent gave 0·128 g (0·5 mmol) of ester *IIIa*, yield 25% and 0·305 g (1·0 mmol) of ester *IIIb*, yield 51%. — *b*) Analogously as under *a*) ester *IIIa* (0·138 g, 0·54 mmol) was prepared from ester *IIa* in a 27% yield, and ester *IIIc* (0·295 g, 0·94 mmol) in a 47% yield.

Bis(2-methoxyethyl) 2-(N-Carboxymethylsulfamoyl)benzoate (*IV*)

A mixture of 2-methoxyethanol (12 ml) and 0·54 g (20 mmol) of calcium hydride was stirred under nitrogen at 115°C for 30 min and ester *IIb* (3·0 g, 10 mmol) was added at once to the solution. The mixture was stirred for 15 min and poured onto a mixture of ice and hydrochloric acid, extracted with chloroform (3 × 30 ml), the extract was washed with water (2 × 100 ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated. The residue was purified by column chromatography on silica gel, using chloroform–methanol as eluent. Yield, 3·15 g (8·4 mmol) of compound *IV* in the form of an oil. For $C_{15}H_{21}NO_8S$ (375·4) calculated: 47·99% C, 5·64% H, 3·73% N, 8·54% S; found: 47·71% C, 5·78% H, 3·48% N, 8·26% S. IR spectrum (cm^{-1}, $CHCl_3$): *v* 3 300 m (NH), 1 668 s, 1 748 s (CO), 1 370 s, 1 183 s (SO_2). ^1H NMR spectrum (δ, C^2HCl_3): 3·14 s (3 H, CH_3), 3·34 s (3 H, CH_3), 3·60 m (2 H, CH_2), 4·10 m (2 H, CH_2), 4·12 s (2 H, CH_2), 7·32 t (1 H, NH), 7·62—7·92 m (4 H, ring protons).

Cyclization Reaction of Ester *IV*

Using the same procedure as in the rearrangement of ester *IIb*, ester *IV* (2·76 g, 7·4 mmol) was reacted with sodium (0·34 g, 14·8 mgatom) and 2-methoxyethanol (8 ml), to yield 1·57 g (5·25 mmol) of ester *IIIb* in a 71% yield.

N-Alkylation of Esters *IIIa*—*IIIc*

A. Catalysis with sodium hydroxide. *a*) A solution of 8·64 g (0·22 mol) of sodium hydroxide in water (60 ml) was added dropwise to a suspension of 49·7 g (0·17 mol) of ester *III*, 27·2 g (0·22 mol) of dimethyl sulfate, benzyltriethylammonium chloride (2·0 g) and 1,2-dichloroethane (150 ml). The addition was carried out under stirring at 20°C, over 40 min. After another 2·5 h the organic layer was separated, the aqueous layer was washed with 1,2-dichloroethane (20 ml) and the combined organic extracts were washed with two 40 ml portions of water, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from ethanol to give 33·8 g (0·11 mol) of compound *Vc*, m.p. 107—109°C (ref.[6] 106—107·5° C), yield 65%. For $C_{13}H_{15}NO_6S$ (313·3) calculated: 49·83% C, 4·83% H, 4·47% N, 11·23% S; found: 497·4% C, 4·78% H, 4·26% N, 10·11% S. IR spectrum (cm^{-1}, KBr): *v* 3 430 m (OH), 1 670 s (CO), 1 385 s, 1 165 s (SO_2). ^1H NMR spectrum (δ, C^2HCl_3): 2·77 s (3 H, CH_3), 3·22 s (3 H, CH_3), 3·50 t (2 H, CH_2), 4·47 t (2 H, CH_2) J = 6 Hz, 7·64—8·06 m (4 H, ring protons), 11·36 s 1 H, OH). — *b*) Using the same procedure as under *a*) ester *IIIa* was converted to ester *Va*, m.p. 168—170°C (ref.[5] 171°C), the spectral characteristics of which are in agreement with the literature data[5]. — *c*) Using the same procedure as under *a*) ester *IIIa* was reacted with diethyl sulfate to give ester *Vb*, m.p. 94—95°C (ref.[8] 97—99°C), yield, 65%. IR spectrum (cm^{-1}, $CHCl_3$): *v* 3 410 w (OH), 1 655 s (CO), 1 360 s, 1 177 s (SO_2). ^1H NMR spectrum (δ, C^2HCl_3): 0·79 t (3 H, CH_3), 3·56 q (2 H, CH_2) J = 7 Hz, 3·90 s (3 H, CH_3), 7·60—8·04 m (4 H, ring protons). — *d*) equally as in the case *a*) ester *IIIc* was converted to ester *Vd*, m.p. 108—111°C (2-propanol), yield 63%. For $C_{14}H_{17}NO_6S$ (327·4) calculated: 51·37% C, 5·23% H, 4·28% N, 9·79% S; found: 51·30% C,

5·11% H, 4·19% N, 9·62% S. IR spectrum (cm^{-1}, $CHCl_3$): 3 320 w (OH), 1 658 s (CO), 1 388 s, 1 181 s (SO_2). ^1H NMR spectrum (δ, C^2HCl_3): 1·20 t, (3 H, CH_3), 2·95 s (3 H, CH_3), 3·54 q (2 H, CH_2), 3·74 t (2 H, CH_2), 4·45 t (2 H, CH_2), 7·55–8·07 m (4 H, ring protons), 11·23 s (1 H, OH).

B. Catalysis with potassium carbonate. A mixture of 3·0 g (10 mmol) of ester *IIIb*, 1·39 g (11 mmol) of dimethyl sulfate, 1·38 g (10 mmol) of potassium carbonate, benzyltriethylammonium chloride (0·1 g), 1,2-dichloroethane (10 ml) and water (2 ml) was stirred at 20°C for 3 h and worked up as under A *a*). Ester *Vd* (1·8 g, 5·75 mmol) was isolated in a 57% yield. – *b*) Equally as under *a*), ester *IIIc* was converted to ester *Vd* in a 52% yield.

4-Hydroxy-2-methyl-N-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (*Ia*)

A. A mixture of 20 g (0·064 mol) of ester *Vc*, 6·6 g (0·07 mol) of 2-aminopyridine and xylene (300 ml) was refluxed and the azeotrope with b.p. 134°C was distilled off continually. After 6 h the boiling temperature of the distillate increased to 139°C. After cooling the product *Ia* was isolated by filtration and crystallized from acetone–heptane. Yield, 20·6 g (0·062 mol) of compound *Ia*, m.p. 200–201°C (ref.[9] 200°C), yield 97%. For $C_{15}H_{23}N_3O_4S$ (331·4) calculated: 54·37% C, 3·95% H, 12·68% N, 9·68% S; found: 54·32% C, 3·86% H, 12·68% N, 9·57% S. IR spectrum (cm^{-1}, Nujol): *v* 3 350 s (OH), 1 630 s (CO), 1 350 s, 1 180 s (SO_2). ^1H NMR spectrum: (δ, hexadeuteriodimethyl sulfoxide): 2·94 s (3 H, CH_3), 7·10 m and 7·64–8·40 m (8 H, ring protons), 8·92 s (1 H, NH), 13·78 s (1 H, OH).

B. Equally as under A ester *Vd* was reacted with 2-aminopyridine in xylene to yield piroxicam *Ia*, m.p. 200·5–201·5°C, in a 92% yield.

4-Hydroxy-2-methyl-N-(5-methyl-3-isoxazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (*Ib*)

A mixture of 6·3 g (20 mmol) of ester *Vc*, 2·16 g (22 mmol) of 3-amino-5-methylisoxazole and xylene (100 ml) was refluxed for 5 h under distilling off the azeotrope with b.p. 134°C. After cooling and filtration compound *Ib* was obtained (5·77 g, 17 mmol), m.p. 256–257°C, decomp. (ref.[11] 258–259°C, decomp.). For $C_{14}H_{13}N_3O_5S$ (335·3) calculated: 50·14% C, 3·91% H, 12·53% N, 9·56% S; found: 50·01% C, 3·81% H, 12·44% N, 9·32% S. IR spectrum (cm^{-1}, KBr): *v* 3 305 s (OH), 1 635 s (CO), 1 350 s, 1 185 s (SO_2). ^1H NMR spectrum (δ, hexadeuteriodimethyl sulfoxide): 2·42 s (3 H, CH_3), 2·82 s (3 H, CH_3), 6·65 s (1 H, CH), 7·46 s (1 H, NH), 7·90–8·05 m (4 H, nucleus), 11·40 s (1 H, OH).

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