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Synthesis of estrogen sulfamates: Compounds with a novel endocrinological profile

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Estrogen sulfamates are promising hormones by oral administration. Therefore, generally applicable and convenient methods for the multigram synthesis of these derivatives are desirable. Numerous estra-1,3,5(10)-trienes derived from estrone, estradiol, 14α,15α-methylenestradiol, ethinylestradiol, and estriol have been esterified with sulfamoyl chloride and N-methylsulfamoyl chloride by a novel approach involving the use of 2,6-di-tert-butylpyridines as bases and chemoselective hydroxy group protections. These pathways circumvent the nonselective formation of esters and side reactions by in situ generated azasulfenes. For toxicological and clinical studies a new synthesis of estrone sulfamate on a 100-g scale was developed using dimethylformamide as the solvent and base. ©1996 by Elsevier Science Inc. (*Steroids* **61**:710–717, 1996)

Keywords: estrogen; sulfamate; 2,6-di-*tert*-butylpyridine; silyl ether

Introduction

Sulfamic acid esters of various groups of compounds show interesting biological activities. Among them are derivatives with anticonvulsant,[1–5] antiviral, and antitrypanosomal[6–8] activities. In addition, sulfamates have been found to be active against glaucoma,[5,9] arthritis,[10] hyperlipidemia,[11,12] and gastric hypersecretion[5] or have shown acetyl coenzyme A transferase[11] or carbonic anhydrase inhibition[5] properties. There are only a few reports on steroid sulfamates. The first synthesized steroid sulfamates are 3-*N,N*-disubstituted esters of ethinylestradiol,[13] which have proved to be considerably stronger estrogens than ethinylestradiol itself.[14] A favorable dissociation between vaginotropic and uterotropic activity has been claimed for *N,N*-disubstituted sulfamates of 1,3-dihydroxy-8α-estra-1,3,5(10)-trienes.[15–17] Sulfamates of estrogenic steroids have been described as sulfatase inhibitors, which may have potential use in the therapy of hormone-dependent breast cancer.[18] Estrone sulfamate administered in combination with dehydroepiandrosterone to rats has been shown to potentiate the memory-enhancing properties of dehydroepiandrosterone sulfate.[19]

In the course of our ongoing search for novel orally active estrogens with improved pharmacokinetic behavior and decreased liver estrogenicity, we have found in animals that estrogens esterified at position 3 by various sulfamic acids have an as yet unrecognized potential to overcome the liver barrier without alteration of important hepatic functions.[20,21] Clinical Phase I studies using the first selected sulfamate have been started very recently. A confirmation of the animal experiments in women may lead to drugs with fundamental benefits in oral contraception and hormone replacement therapy.

As part of our investigations, we synthesized numerous structurally modified estrogen 3-sulfamates. We report here on the synthesis of the corresponding esters derived from estrone, 17β-estradiol, 17α-estradiol, 14α,15α-methylenestradiol, ethinylestradiol, and estriol.

Experimental

General methods

^{1}H NMR spectra were recorded in dimethyl sulfoxide-d_6 (unless stated otherwise) on a Varian Gemini 300 (300 MHz). Chemical shifts are reported as δ-values in ppm downfield from tetramethylsilane as the internal standard; *J* values are given in Hertz. Melting points were measured with Boetius equipment. Optical rotations were taken with the Polamat A (Carl Zeiss Jena), $c = 1$ g/100 mL, temperature +20°C; values are given in 10^{-1} deg cm^2 g^{-1}. Chromatography was performed on silica gel (Kieselgel 60; Merck

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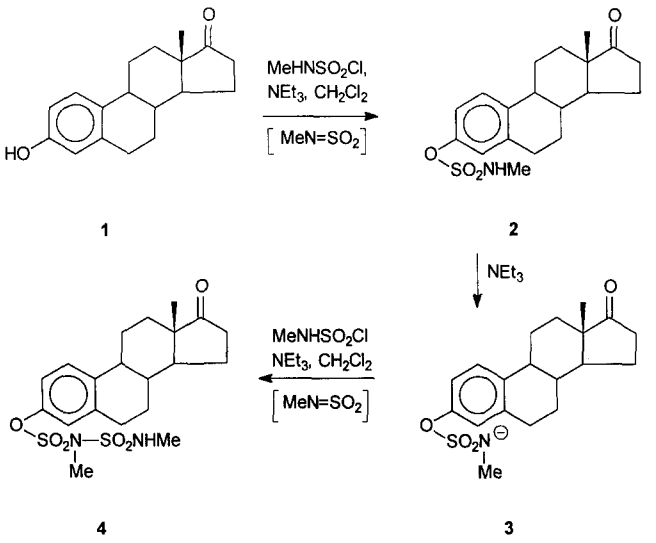
Table 1 Physical and spectroscopic data of sulfamates and intermediates

Compd.	M.p.	[α]D	^{1}H NMR
2	193–196	+63[a]	0.91 (s, 3 H, 18–H), 2.95 (d, ^3J = 5.2, 3 H, NHC$\underline{H}_3$), 4.57 (q, ^3J = 5.2, 1 H, NHC$\underline{H}_3$), 7.03 (d, ^4J = 3.0, 1 H, 4–H), 7.05 (dd, ^3J = 8.1, ^4J = 3.0, 1 H, 2–H), 7.30 (d, ^3J = 8.1, 1 H, 1–H)[c]
5	194–198	+33.5[a]	0.78 (s, 3 H, 18–H), 2.94 (d, ^3J = 5.3, 3 H, NHC$\underline{H}_3$), 3.74 (t, ^3J = 8.3, 1 H, 17–H), 4.54 (q, ^3J = 5.3, 1 H, NHC$\underline{H}_3$), 7.00 (d, ^4J = 2.6, 1 H, 4–H), 7.04 (dd, ^3J = 8.5, ^4J = 2.6, 1 H, 2–H), 7.30 (d, ^3J = 8.5, 1 H, 1–H)[c]
6	199–202	+128[a]	0.84 (s, 3 H, 18-H), 6.99 (d, ^4J = 2.4, 1 H, 4–H), 7.03 (dd, ^3J = 8.4, ^4J = 2.4, 1 H, 2–H), 7.36 (d, ^3J = 8.4, 1 H, 1–H), 7.95 (s, 2 H, –N$\underline{H}_2$)
7	204–206	+61[a]	0.67 (s, 3 H, 18–H), 3.53 (td, ^3J = 8.2, ^3J = 4.7, 1 H, 17–H), 4.65 (d, ^3J = 4.7, 1 H, 17–OH), 6.96 (d, ^4J = 2.6, 1 H, 4–H). 7.02 (dd, ^3J = 8.6, ^4J = 2.6, 1 H, 2–H), 7.35 (d, ^3J = 8.6, 1 H, 1–H), 7.91 (s, 2 H, –N$\underline{H}_2$)
9	183–186	+59[b]	0.84 (s, 3 H, 18–H), 3.77 (s, 3 H, –OC$\underline{H}_3$, 6.99 (s, 1 H, 4–H). 7.00 (s, 1 H, 1–H), 7.82 (s, 2 H, –N$\underline{H}_2$)
11	191–195	+66[a]	0.99 (s, 3 H, 18–H), 3.20 (s, 3 H, –OC$\underline{H}_3$), 4.24 (m, 1 H, 11–H), 6.97 (d, ^4J = 2.4, 1 H, 4–H), 7.02 (dd, ^3J = 8.6, ^4J = 2.4, 1 H, 2–H), 7.26 (d, ^3J = 8.6, 1 H, 1–H), 7.93 (s, 2 H, –N$\underline{H}_2$)
13	217–223	+115[b]	0.84 (s, 3 H, 18–H), 6.32 (d, ^3J = 5.4, 1 H, 11–H), 7.02 (d, ^4J = 2.6, 1 H, 4–H), 7.04 (dd, ^3J = 8.5, ^4J = 2.6, 1 H, 2–H), 7.71 (d, ^3J = 8.5, 1 H, 1–H), 7.95 (s, 2 H, –N$\underline{H}_2$)
14	195–198	+44[b]	0.68 (s, 3 H, 18–H), 3.63 (td, ^3J = 8.0, ^3J-5.0, 1 H, 17–H), 4.61 (d, ^3J = 5.0, 1 H, 17–OH), 6.31 (d, ^3J = 4.9, 1 H, 11–H), 6.98 (d, ^4J = 2.6, 1 H, 4–H), 7.02 (dd, ^3J = 8.7, ^4J = 2.6, 1 H, 2–H), 7.69 (d, ^3J = 8.7, 1 H, 1–H), 7.92 (s, 2 H, –N$\underline{H}_2$)
16	176–180	+107[b]	0.70 (s, 3 H, 18–H), 5.52 (s, 1 H, 7–H), 7.04 (d, ^4J = 2.3, 1 H, 4–H), 7.08 (dd, ^3J = 8.7, ^4J = 2.3, 1 H, 2–H), 7.36 (d, ^3J = 8.7, 1 H, 1–H), 7.93 (s, 2 H, –N$\underline{H}_2$)
17	197–202	+136[b]	0.53 (s, 3 H, 18–H), 3.67 (td, ^3J = 8.4, ^3J = 5.0, 1 H, 17–H), 4.57 (d, ^3J = 5.0, 1 H, 17–OH), 5.35 (s, 1 H, 7–H), 7.01 (d, ^4J = 2.7, 1 H, 4–H), 7.07 (dd, ^3J = 8.3, ^4J = 2.7, 1 H, 2–H), 7.34 (d, ^3J = 8.3, 1 H, 1–H), 7.92 (s, 2 H, –N$\underline{H}_2$)
19	224–227	+39.5[b]	0.68 (s, 3 H, 18–H), 7.41 (d, ^3J = 8.5, 1 H, 7–H), 7.46 (dd, ^3J = 9.0, ^4J = 2.6, 1 H, 2–H), 7.79 (d, ^4J = 2.6, 1 H, 4–H), 7.84 (d, ^3J = 8.5, 1 H, 6–H), 8.03 (s, 2 H, –N$\underline{H}_2$), 8.07 (d, ^3J = 9.0, 1 H, 1–H)
20	199–202	+37[b]	0.55 (s, 3 H, 18–H), 3.77 (td, ^3J = 8.1, ^3J = 4.5, 1 H, 17–H), 4.70 (d, ^3J = 4.5, 1 H, 17–OH), 7.25 (d, ^3J = 8.8, 1 H, 7–H), 7.42 (dd, ^3J = 9.3, ^4J = 2.7, 1 H, 2–H), 7.75 (d, ^4J = 2.7, 1 H, 4–H), 7.76 (d, ^3J = 8.8, 1 H, 6–H), 8.03 (s, 2 H, –N$\underline{H}_2$), 8.05 (d, ^3J = 9.3, 1 H, 1–H)
23	Decomp.		3.01 (s, 3 H, N–C$\underline{H}_3$), 3.26 (s, 3 H, N–C$\underline{H}_3$), 8.35 (s, 1 H, –C$\underline{H}$=), 11,47 (br, 1 H, =N$\underline{H}^{\oplus}$–)
25	84–85	–1[b]	0.04 (s, 6 H, Si–C$\underline{H}_3$), 0.19 (s, 6 H, Si–C$\underline{H}_3$), 0.66 (s, 3 H, 18–H), 0.90 (s, 9 H, ^{t}–But), 0.97 (s, 9 H, ^{t}–But), 3.71 (d, ^3J = 5.6, 1 H, 17–H), 6.55 (d, ^4J = 2.8, 1 H, 4–H), 6.61 (dd, ^3J = 8.3, ^4J = 2.8, 1 H, 2–H), 7.14 (d, ^3J = 8.3, 1 H, 1–H)
26	161–162	–1.5[b]	0.03 (s, 6 H, Si–C$\underline{H}_3$), 0.64 (s, 3 H, 18–H), 0.87 (s, 9 H, ^{t}–But), 3.72 (d, ^3J = 5.4, 1 H, 17–H), 6.43 (d, ^4J = 2.7, 1 H, 4–H), 6.50 (dd, ^3J = 8.1, ^4J = 2.7, 1 H, 2–H), 7.06 (d, ^3J = 8.1, 1 H, 1–H), 9.01 (s, 1 H, 3–OH)
27	159–160	–1[b]	0.04 (s, 6 H, Si–C$\underline{H}_3$), 0.65 (s, 3 H, 18–H), 0.88 (s, 9 H, ^{t}–But), 3.74 (d, ^3J = 5.3, 1 H, 17–H), 6.96 (d, ^4J = 2.6, 1 H, 4–H), 7.01 (dd, ^3J = 8.4, ^4J = 2.6, 1 H, 2–H), 7.36 (d, ^3J = 8.4, 1 H, 1–H), 7.90 (s, 2 H, –N$\underline{H}_2$), 9.01 (s, 1 H, 3–OH)
28	192–196	+22[b]	0.62 (s, 3 H, 18–H), 3.59 (d, ^3J = 6.0, 1 H, 17–H), 4.38 (s, 1 H, 17–OH), 6.96 (d, ^4J = 2.7, 1 H, 4–H), 7.02 (dd, ^3J = 8.5, ^4J = 2.7, 1 H, 2–H), 7.36 (d, ^3J = 8.5, 1 H, 1–H), 7.88 (s, 2 H, –N$\underline{H}_2$),
30	193–197	–50[b]	0.59 (s, 3 H, 18–H), 3.68 (dd, ^3J = 5.9, ^3J = 4.6, 1 H, 17–H), 4.46 (d, ^3J = 4.6, 1 H, 17–OH), 7.02 (d, ^4J = 2.9, 1 H, 4–H), 7.05 (dd, ^3J = 8.5, ^4J = 2.9, 1 H, 2–H), 7.23 (d, ^3J = 8.4, 1 H, 1–H), 7.91 (s, 2 H, –N$\underline{H}_2$)
34	189–194	–71[b]	0.39 (dd, ^2J = 3.5, ^3J = 8.2, 1 H, 14,15–C$\underline{H}_2$), 0.83 (s, 3 H, 18–H), 1.35 (t, ^2J = 3.5, 1 H, 14,15–C$\underline{H}_2$), 3.71 (d, ^3J = 6.1, 1 H, 17–H), 4.63 (s, 17–OH), 7.00 (d, ^4J = 2.3, 1 H, 4–H), 7.05 (dd, ^3J = 8.5, ^4J = 2.3, 1 H, 2–H), 7.21 (d, ^3J = 8.4, 1 H, 1–H), 7.85 (s, 2 H, –N$\underline{H}_2$)
36	210–214	+58[b]	0.26 (dd, ^2J = 5.7, ^3J = 3.0, 1 H, 14,15–C$\underline{H}_2$), 0.39 (dd, ^2J = 5.7, ^3J = 8.0, 1 H, 14,15-C$\underline{H}_2$), 0.89 (s, 3 H, 18–H), 3.40 (dd, ^3J = 9.1, ^3J = 7.1, 1 H, 17–H), 4.44 (s, 17–OH), 6.96 (d, ^4J = 2.6, 1 H, 4–H), 7.03 (dd, ^3J = 8.7, ^4J = 2.6, 1 H, 2–H), 7.39 (d, ^3J = 8.7, 1 H, 1–H), 7.90 (s, 2 H, –N$\underline{H}_2$)
37	192–193	+56[a]	0.19 (dd, ^2J = 5.1, ^3J = 8.0, 1 H, 14,15–C$\underline{H}_2$), 0.26 (dd, ^2J = 5.1, ^3J = 2.7, 1 H, 14,15–C$\underline{H}_2$), 0.89 (s, 3 H, 18–H), 2.71 (d, ^3J = 3.8, 3 H, NHC$\underline{H}_3$), 3.39 (ddd, ^3J = 9.2, ^3J = 7.0, ^3J = 5.5, 1 H, 17–H), 4.43 (d, ^3J = 5.5, 1 H, 17–OH), 6.96 (d, ^4J = 2.7, 1 H, 4 = H), 7.03 (dd, ^3J = 8.8, ^4J = 2.7, 1H, 2–H), 7.39 (d, ^3J = 8.8, 1 H, 1–H), 8.12 (d, ^3J = 4.8, 1 H, –N$\underline{H}$)
40	209–211	–15[b]	0.77 (s, 3 H, 18–H), 3.33 (s, 1 H, –C≡C$\underline{H}$), 5.37 (s, 1 H, 17–OH), 6.96 (d, ^4J = 2.6, 1 H, 4–H), 7.02 (dd, ^3J = 8.7, ^4J = 2.6, 1 H, 2–H), 7.35 (d, ^3J = 8.7, 1 H, 1–H), 7.89 (s, 2 H, –N$\underline{H}_2$)
41	156–162	+2[a]	0.88 (s, 3 H, 18–H), 2.61 (s, 1 H, –C≡C$\underline{H}$), 2.94 (d, ^3J = 5.5, 3 H, –NHC$\underline{H}_3$), 4.54 (q, ^3J = 5.1, 1 H, –N$\underline{H}$), 7.00 (d, ^4J = 2.7, 1 H, 4–H), 7.04 (dd, ^3J = 8.6, ^4J = 2.7, 1 H, 2–H), 7.31 (d, ^3J = 8.6, 1 H, 1–H)[c]
47	208–213	+13[b]	0.67 (s, 3 H, 18–H), 3.30 (dd, ^3J = 5.9, ^3J = 4.7, 1 H, 16–H), 3.84 (ddd, ^3J = 9.1, ^3J = 5.7, ^3J = 4.7, 1 H, 17–H), 4.63 (d, ^3J = 4.7, 1 H, –OH), 4.70, (d, ^3J = 4.7, 1 H, –OH), 6.95 (d, ^4J = 2.6, 1 H, 4–H), 7.01 (dd, ^3J = 8.8, ^4J = 2.6, 1 H, 2–H), 7.32 (d, ^3J = 8.8, 1 H, 1–H), 7.89 (s, 2 H, –N$\underline{H}_2$)
48	199–202	+26[a]	0.67 (s, 3 H, 18–H), 2.70 (s, 3 H, –NHC$\underline{H}_3$), 3.30 (d, ^3J = 5.5, 1 H, 16–H), 3.84 (dd, ^3J = 9.4, ^3J = 5.1, 1 H, 17–H), 6.95 (d, ^4J = 2.6, 1 H, 4–H), 7.01 (dd, ^3J = 8.8, ^4J = 2.6, 1 H, 2–H), 7.33 (d, ^3J = 8.8, 1 H, 1–H)

[a]Dioxane.
[b]Pyridine.
[c]Chloroform-d.



Scheme 1 Reaction of estrone with *N*-methylsulfamoyl chloride/triethylamine.

A.G. Darmstadt; 0.04–0.063 mm), using steroid:adsorbent (1:100 by weight).

Estra-1,3,5(10)-trien-3-yl sulfamates: general procedure. To a solution of an estra-1,3,5(10)-trien-3-ol (1 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) or 2,6-di-*tert*-butylpyridine (DTBP) (3 mmol each) in CH_2Cl_2 (16 mL) was added sulfamoyl chloride or *N*-methylsulfamoyl chloride (6 mmol) portionwise with stirring. After 15–30 min the ester formation reached completion (thin-layer chromatography, TLC). The solution was now washed until neutral with water, dried over anhydrous Na_2SO_4, and rotary evaporated. Purification of the residue by chromatography and crystallization from a suitable solvent (acetone/hexane in most cases) gave the title compounds (yield: 65–85%). The following sulfamates have been prepared by this protocol: **2, 6, 9, 11, 13, 16, 19, 28, 30, 34, 36, 37, 40, 41, 47, 48.**

17-Oxo-estra-1,3,5(10)-trien-3-yl sulfamate (6). Estrone (30 g, 0.11 mol) was dissolved in anhydrous dimethylformamide (DMF) (500 mL). To the cooled solution (+10 to +15°C) was added sulfamoyl chloride (64.2 g, 0.55 mol) for 20 min with stirring while keeping the temperature below +30°C. After several minutes a white precipitate (**23**) was formed. The mixture was stirred at room temperature for another 12 h and then quenched by the addition of H_2O (1.5 L). The suspension was cooled to +15°C, stirred for 1 h, and filtered. The crystals were washed neutral with water, dried, and crystallized from acetone to obtain the title compound **6** (yield: 80%).

Reduction of 17-oxo-estra-1,3,5(10)-trien-3-yl sulfamates: general procedure. To a cold (0°C) solution of a 17-oxo-estra-1,3,5(10)-trien-3-yl sulfamate (1 mmol) in MeOH (5–7 mL) and THF (5–7 mL), $NaBH_4$ (3.3 mmol) was added in portions with stirring. After 30 min, TLC showed the reduction to be quantitative. Thereafter, AcOH was added dropwise to adjust the pH to 6, and the solution was concentrated by rotary evaporation (bath temperature 50°C). The addition of H_2O, filtration, and crystallization gave the 17β-hydroxy-estra-1,3,5(10)-trien-3-yl sulfamate (yield: 90–93%). The following compounds have been prepared by this method: **5, 7, 14, 17, 20.**

17-Oxo-estra-1,3,5(10)-trien-3-yl [*N*-methyl-*N*-(*N'*-methylsulfamoyl)]sulfamate (4). Estrone (3 g: 11.1 mmol) was dissolved in a mixture of CH_2Cl_2 (1.2 L) and Et_3N (28.2 mL, 203 mmol). *N*-Methylsulfamoyl chloride (3 mL, 34 mmol) was added for 10 min with stirring. Stirring was continued for 1.5 h, whereupon TLC showed quantitative transformation of estrone into sulfamates **2** and **4.** The solution was concentrated (600 mL) by rotary evaporation; washed in turn with H_2O, diluted HCl, and H_2O; dried over anhydrous Na_2SO_4; and rotary evaporated to dryness. Repeated crystallization of the crude product from acetone/hexane yielded sulfamate **2.** The mother liquors of these crystallizations were combined, rotary evaporated, and subjected to column chromatography (eluent toluene: chloroform: methanol, 80:15:5). The fractions containing the sulfamate **4** were collected and rotary evaporated, and the residue was twice crystallized from acetone/hexane to give the title compound (yield: 0.54 g, 11%).

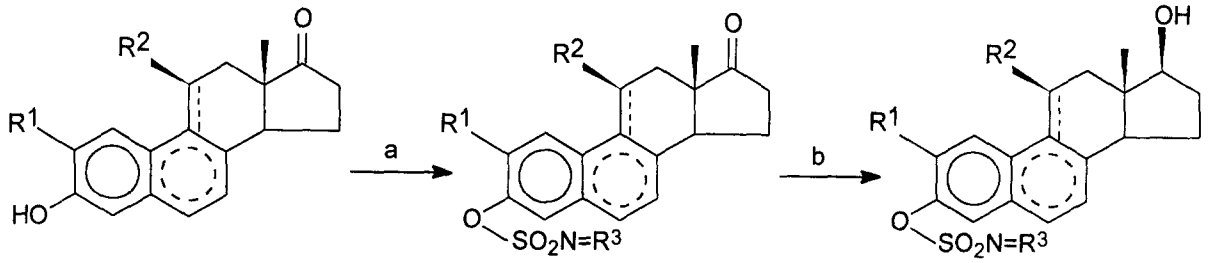
All compounds reported herein had satisfactory elemental

Table 2 Esterification of ethinylestradiol trimethylsilyl ether **(38)** with *N*-methylsulfamoyl chloride in the presence of various bases

Base (equiv.)	$MeNH\text{-}SO_2Cl$ (equiv.)	Solvent	Ethinyl-estradiol[a]	Sulfamate **41**[a,b]	Sulfamoyl sulfamate **42**[a,b]
Triethylamine (6)	(3)	CH_2Cl_2	0.4	58	29
Pyridine (6)	(3)	CH_2Cl_2	0.04	65	23
DBN[c] (12)	(9)	CH_2Cl_2	1	72	7
DABCO[d] (6)	(3)	CH_2Cl_2	0.6	63	29
DMAP[e] (0.1)	(4.5)	Pyridine	9	76	—
DBMP[f] (6)	(3)	CH_2Cl_2	0.05	98	0.1

[a]Relative area percentages found by HPLC.
[b]Upon hydrolysis of the silylether group.
[c]1,5-Diazabicyclo [4.3.0]non-5-ene.
[d]1,4-Diazabicyclo[2.2.2]octane.
[e]4-Dimethylaminopyridine.
[f]2,6-Di-*tert*-butyl-4-methylpyridine.

Table 3 Sulfamates derived from estrone, estradiol, equilin, and equilenin.



1, 8, 10, 12, 15,18 **2, 4, 6, 9, 11, 13, 16, 19, 21** **5, 7, 14, 17, 20, 21**

(a) ^{3}R=N-SO_2Cl (6 equiv.), DBMP or DTBP (3 equiv.), CH_2Cl_2, +23°C, 2 h; (b) $NaBH_4$ (3.3 equiv.), MeOH/THF, +5°C, 15 min.

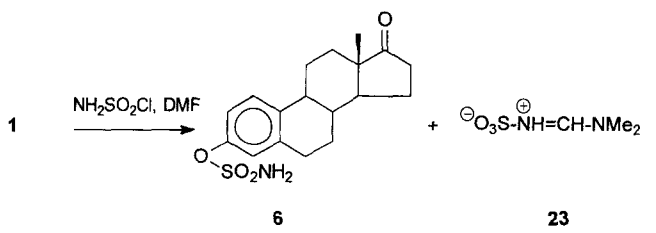
Compd.	R^1	R^2	R^3	Compd.	R^1	R^2	R^3	Δ
1	H	H		**12**	H	OH		
2	H	H	H, Me	**13**	H	H	H, H	9(11)
4	H	H	Me, SO_2–NH–Me	**14**	H	H	H, H	9(11)
5	H	H	H, Me	**15**	H	H		7
6	H	H	H, H	**16**	H	H	H, H	7
7	H	H	H, H	**17**	H	H	H, H	7
8	MeO	H		**18**	H	H		6,8
9	MeO	H	H, H	**19**	H	H	H, H	6,8
10	H	MeO		**20**	H	H	H, H	6,8
11	H	MeO	H, H	**21**	H	H	=CH–NMe_2	

analysis and spectral data that were consistent with the structures shown. The ^{1}H NMR and mass spectra have proved to be considerably relevant to the structure elucidation of the sulfamates. The spectra of *N*-methyl-sulfamates **2, 5, 37, 41** and **48,** measured in chloroform-*d,* displayed signals at 2.9 ppm (3 H, d, J = 5.1 Hz) and 4.5 ppm (1 H, q, J = 5.1 Hz), originating from the CH_3–NH–SO_2-group. Addition of water-d_2 quenched the NH signal and led to a CH_3–N< singlet. The spectra of the N-unsubstituted sulfamates **6, 7, 9, 11, 13, 14, 16, 17, 19, 20, 27, 28, 30, 32–34, 36, 40,** and **47** showed highly characteristic NH_2 singlets at 7.9 ppm in DMSO-d_6 that were quenched upon addition of water-d_2 (Table 1).

All sulfamates recorded gave molecular ions of moderate intensities by mass spectrometry. Dominating ions in the spectra of phenol sulfamates arose from extrusion of azasulfene or *N*-methylazasulfene. In contrast, the ester of the aliphatic 17-hydroxy group showed loss of sulfamic acid.

Results and discussion

Esterification of aromatic steroids by *N,N*-dialkylsulfamoyl chlorides is known to take place in a very facile and completely chemoselective manner at the phenolic hydroxy group by phase transfer catalysis (PTC).[22] However, the PTC reaction of aromatic steroids with *N*-methyl and *N,N*-unsubstituted sulfamoyl chlorides[23] gave insufficient results in our hands. Because of our continuing demand for *N*-methyl and *N,N*-unsubstituted estrogen sulfamates for detailed endocrinological and toxicological investigations, we have been studying alternative methods for the synthesis of these esters on a 1- to 100-g scale.



6 23

Scheme 2 Reaction of estrone (**1**) with sulfamoyl chloride in DMF.

When estrone (**1**) was allowed to react with *N*-methylsulfamoyl chloride[24] in dichloromethane solution in the presence of triethylamine, a rapid and complete reaction occurred to give a mixture of the desired *N*-methylsulfamate **2** and sulfamoyl sulfamate **4** in a ratio of 1.7:1 (Scheme 1). The sulfamoylation of other estra-1,3,5(10)-trien-3-ols in the presence of triethylamine also suffered from sulfamoyl sulfamate formation. Since the separation of the corresponding esters proved rather difficult because of nearly identical solubilities and polarities, a detailed screening for bases with a higher selectivity was performed using ethinylestradiol 17-trimethylsilyl ether (**38**) (vide infra, Scheme 4) as starting material. Table 2 shows the results which were obtained when compound **38** was allowed to react with *N*-methylsulfamoyl chloride in the presence of various bases. It was found that the formation of compound **42** was nearly completely suppressed and ester **41** nearly quantitatively formed when the esterification was run in the presence of DBMP as base. The cheaper base, DTBP (2,6-di-tert-butylpyridine), worked equally well.

The dehydrohalogenation of N-monosubstituted sulfamoyl chlorides with triethylamine to give strong electrophilic azasulfenes has been reported.[25,26] Perhaps estrogen sulfamates are formed with N-methylsulfamoyl chloride in the presence of triethylamine by an elimination-addition

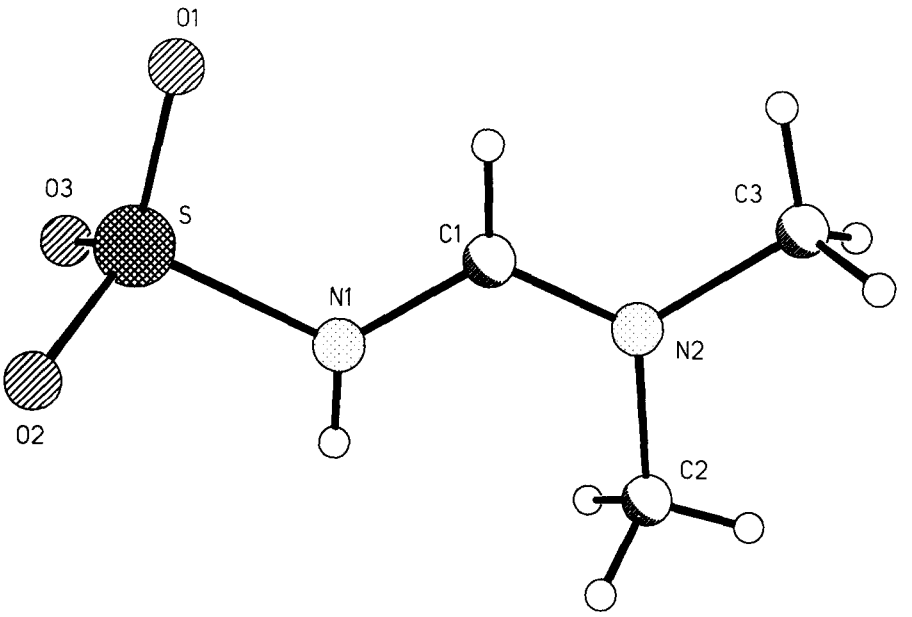
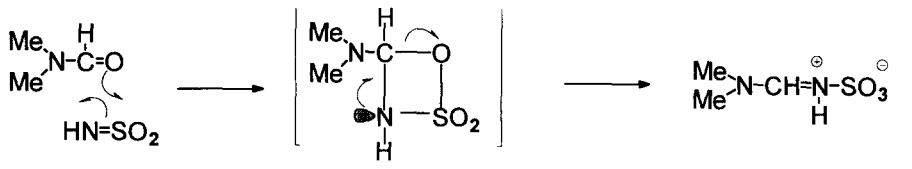


Figure 1 Crystal structure of compound **23.**

pathway rather than by substitution. For example, the ester **2,** once formed, is assumed to be deprotonated at nitrogen by triethylamine to give the nucleophile **3,** which is attacked by additional *N*-methylsulfamoyl chloride or *N*-methylazasulfene, providing by-product **4** (Scheme 1). The highly hindered pyridine bases DBMP and DTBP, capable of binding hydrogen chloride originating from the esterification of **1,** are thought to be incapable of abstracting the proton at the sulfamate group of ester **2.** Thus formation of sulfamoyl sulfamate **4** caused by DBMP or DTBP is a very minor pathway. (For a discussion of the unusual chemical characteristics of 2,6-di-*tert*-butylpyridine, see Ref. 27.)

Esterification of estrone (**1**) and of the estrone derivatives **8, 10, 15,** and **18** by N,N-unsubstituted sulfamoyl chloride[28,29]/DBMP or DTBP in dichloromethane was equally successful, yielding the esters **6, 9, 11, 16** and **19** in 65–80% yield (Table 3). Esterification of 11β-hydroxyestrone (**12**) was accompanied by water elimination furnishing the 9(11)-dehydro derivative **13.** When estradiol was allowed to react analogously with sulfamoyl chloride, esterification at position 17 took place predominantly and the 17β-sulfamate was formed. Because of this unexpected chemoselective reaction the estradiol esters **5, 7, 14, 17,** and **20** have been prepared via the corresponding estrone derivatives **2, 6, 13, 16,** and **19** by reduction with sodium borohydride, a reaction that did not attack the sulfamate moiety. (By using more rigorous reduction systems, e.g., alkali metal in liquid ammonia, the sulfamate group is hydrogenolytically cleaved.)

Later on, estradiol-3-sulfamate (**7**) was selected for initial toxicological and clinical studies. For this reason, efforts were made to synthesize compound **7** on a multigram (100-g) scale. Estrone is sparingly soluble in dichloromethane, and the separation of large amounts of DBMP or DTBP from the ester **6** has proved laborious. Therefore, an alternative protocol for the synthesis of estrone ester **6** was required. Studying DMF as the solvent for estrone, we first used the recently described esterification via the estrone sodium salt, formed by reaction with sodium hydride.[18] However, caused by reaction with DMF, product **6** was contaminated by varying amounts of azomethine **21.** Afterwards, we were pleased to find that sulfamoylation of estrone succeeded in DMF without any additional base. Thus the addition of sulfamoyl chloride to estrone dissolved in DMF yielded 80% sulfamate **6** after a reaction time of 12 h. As result of a competing reaction between sulfamoyl chloride and DMF the N-methylensulfamic acid **23** was formed as a second product (Scheme 2). However, since **23** precipitated from the reaction mixture and was highly soluble in water, pure ester **6** was easily isolated. The structure of **23** followed from IR data (very strong CH = N vibration) and



22 **23**

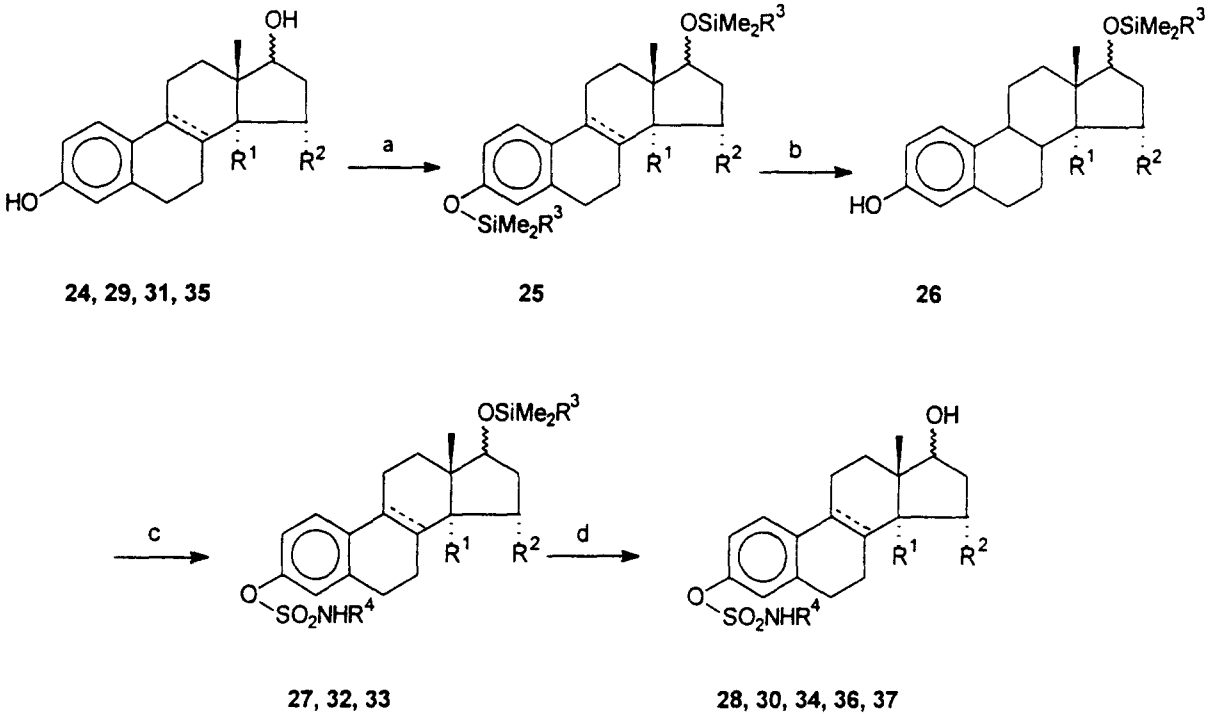
Scheme 3 Proposed mechanism for the reaction between azasulfene and DMF.

^{1}H NMR measurement $(CH_3)_2N$ signals and a downfield shifted singlet for the –CH= proton). Ultimate confirmation of structure **23** resulted from an x-ray diffraction analysis (Figure 1). As depicted in Scheme 3, compound **23** may be formed by the electrophilic addition of azasulfene, derived from sulfamoyl chloride, to the negatively charged carbonyl oxygen of DMF to give the (probably instable) cyclic intermediate **22,** which subsequently rearranges to compound **23.**

Another focus was on sulfamates derived from 17α-estradiol **(24),** 8,9-bisdehydro **24 (29),** 14,15-methylene **29 (31),**[30] and 14,15-methylenestradiol **(35)**[30,31] (Table 4). Silyl ether technology was a useful tool for the synthesis of starting material with a protected 17-hydroxy group. Thus the bis-*tert*-butyldimethylsilyl (TBS) ether **25** was exposed for 1 h to 1 equivalent tetrabutylammonium fluoride (TBAF) in tetrahydrofuran to give phenol **26** quantitatively, which was converted to sulfamate **27** using DBMP as base. The 17-silyl ether was then cleaved by a mixture of acetic acid:water:tetrahydrofuran (3:1:1) for 3 days at +23°C to afford the desired compound **28** (attempted cleavage with TBAF suffered from preferred ester hydrolysis at C-3). Whereas sulfamates **30, 36,** and **37** were obtained by the same approach, the TBS ether **32** completely resisted hydrolysis by aqueous acetic acid. This can be explained by the presence of the 14α,15α-methylene bridge blocking the α-side attack of the reagent. Fortunately, when trimethylsilyl ether protection was applied, ether **33** was readily hydrolyzed to yield sulfamate **34.**

The synthesis of the ethinylestradiol sulfamates **40** and **41** has been accomplished analogously, starting with trimethylsilyl ether **38** (Scheme 4).[32] Protection of the 17-hydroxy group was essential, since the unprotected ethinylestradiol, when reacted with sulfamoyl chloride in the pres-

Table 4 Sulfamates derived from 17α-estradiol and 14α, 15α-methylenestradiol.

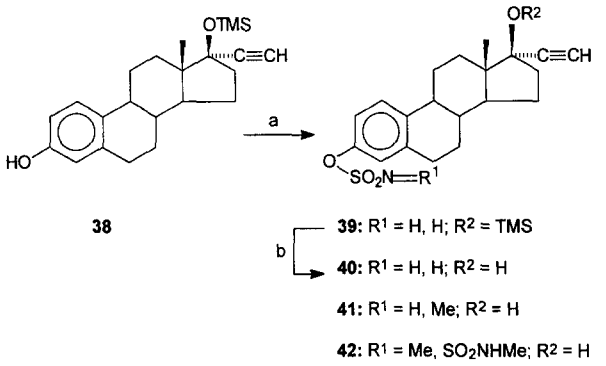


24, 29, 31, 35 **25** **26**

27, 32, 33 **28, 30, 34, 36, 37**

(a) TBSCl (6.9 equiv.), ImH (12 equiv.), DMF, +23°C, 18 h; (b) TBAF.3H_2O (1 equiv.), THF, +23°C, 10 min; (c) R^4HN-SO_2Cl (6 equiv.), TBMP (3 equiv.), CH_2Cl_2, +23°C, 2 h; (d) AcOH:H_2O:THF, 3:1:1, +23°C, 5 d.

Compd.	R^1 R^2	R^3	R^4	17-ξ	Δ	Compd.	R^1 R^2	R^3	R^4	17-ξ	Δ
24	H, H			α		**31**	CH_2			α	8
25	H, H	*t*-Bu		α		**32**	CH_2	*t*-Bu	H	α	8
26	H, H	*t*-Bu		α		**33**	CH_2	Me	H	α	8
27	H, H	*t*-Bu	H	α		**34**	CH_2		H	α	8
28	H, H		H	α		**35**	CH_2			β	
29	H, H			α	8	**36**	CH_2		H	β	
30	H, H		H	α	8	**37**	CH_2		Me	β	

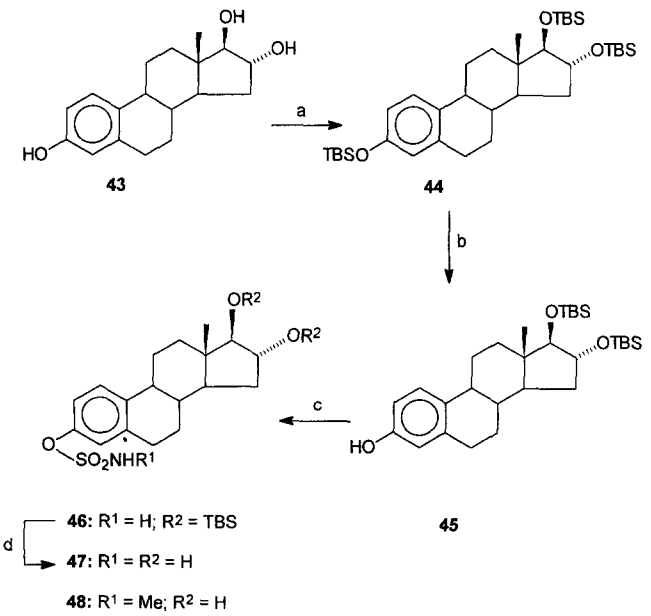


Scheme 4 Synthesis of ethinylestradiol 3-sulfamates; (a) R^1NH-SO_2Cl (6 equiv.), TBMP (3 equiv.), CH_2Cl_2, +23°C, 1.5 h; (b) HCl:H_2O, 1:1, stirring for 8 h, +23°C.

ence of triethylamine, gave a side chain rearranged ester, whereas addition of the base DBMP led partly to unstable disulfamates.

The approach to estriol sulfamate **47** (Scheme 5) involved formation of the tris-TBS ether **44** from estriol **(43),** chemoselective ether deprotection by controlled treatment with TBAF in tetrahydrofuran to give phenolic steroid **45,** esterification **(46),** and 16,17-diether deprotection using the acetic acid/water/tetrahydrofuran mixture. *N*-Methylsulfamate **48** was obtained as well.

In summary, we found a novel, generally applicable approach to the synthesis of 3-sulfamates derived from naturally occurring estrogens and derivatives thereof. The described pathway includes the use of 2,6-di-*tert*-butylpyridines as base and selective silyl ether formation in case of multiple hydroxylated steroids. The synthesis of estrone-3-sulfamate **(6)** was accomplished by esterification of estrone **(1)** in DMF, which worked as solvent and base as well.



Scheme 5 Synthesis of estriol 3-sulfamates; (a)–(d), see Table 4.

Acknowledgment

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References

1. Maryanoff BE, Gardocki JF, inventors; McNeilab, Inc., assignee. Anticonvulsant sulfamate derivatives. US patent 4 513 006. 1983 Sep 26.
2. Maryanoff BE, Nortey SO, inventors; McNeilab, Inc., assignee. Anticonvulsant phenylethyl sulfamates, pharmaceutical compositions containing them, and their use. US Patent 4 792 569. 1987 Aug 27.
3. Lo YS, Walsh DA, Uwaydah IM, inventors; Robins AH Co., Inc., assignee. Preparation of phenyl and phenoxyethyl sulfamates and analogs as anticonvulsants. US Patent 5 025 031. 1989 Nov. 30.
4. Costanzo MJ, Maryanoff BE, inventors; McNeilab, Inc., assignee. Preparation of anticonvulsant sorbopyranose sulfamates. WO 94/14 827 A1. 1994 Jul 7.
5. Maryanoff BE, Constanzo MT, Shank RP, Schupsky TT, Ortegon ME, Vaught TL (1993). Anticonvulsant sugar sulfamates. Potent cyclic sulfate and cyclic sulfite analogues of topiramate. *Bioorg Med Chem Lett* **3**:2565–2656.
6. Camarasa MJ, Fernandez-Resa P, Garcia-Lopez MT, De-las-Heras F (1985). Uridine 5′-diphosphate glucose analogs. Inhibitors of protein glycosylation that show antiviral activity. *J Med Chem* **28**:40–46.
7. Smee DF, Alaghamandan HA, Kini GD, Robins RK (1988). Antiviral activity and mode of action of ribavirin 5′-sulfamate against Semliki forest virus. *Antiviral Res* **10**:253–262.
8. Kini GD, Henry EM, Robins RK, Larson SB, Marr TT, Berens RL, Bacchi CT, Nathan HC, Keithly TS (1990). Synthesis, structure, and antiparasitic activity of sulfamoyl derivatives of ribavirin. *J Med Chem* **33**:44–48.
9. Lo YS, Nolan JC, Shamblee DA, inventors; Robins AH Co., Inc., assignee. Sulfamates as antiglaucoma agents. US Patent 5 192 785. 1989 Sep 3.
10. Nolan JC, Walsh DA, Lo Y, Gathright CE, Radvany CH, Foxwell M, Wrightman L, Graff G, Sancili LF (1990). AHR-15010—a novel anti-arthritic agent. *J Pharm Pharmacol* **42**:533–537.
11. Lee HT, Picard JA, Sliskovic DR, Wierenga W inventors; Warner-Lambert Co., assignee. N-Acyl sulfamic acid esters (or thioesters), n-acyl sulfonamides, and N-sulfonyl carbamic acid esters (or thioesters) as hypercholesterolemic agents. WO 94/26 702 A1. 1994 Nov 24.
12. Picard JA, Sliskovic DR, inventors; Warner-Lambert Co., assignee. Preparation of N-(aryloxysulfonyl)urea derivatives as acylcoenzyme A: cholesterol acyltransferase (ACAT) inhibitors. WO 92/08692 A1. 1992 May 29.
13. Schwarz S, Weber G, Kühner F (1970). Sulfamate des 17α-Äthinylöstradiols. *Z Chem* **10**:299–300.
14. Stölzner W (1989). Tierexperimenteller Beitrag zur Entwicklung estrogener Wirkstoffe, Dissertation, Friedrich Schiller University Jena.
15. Prezewowsky K, Laurent H, Hofmeister H, Wiechert R, Neumann F, Nishino Y inventors; Schering A.-G., assignee. 1,3-Oxygenated 8α-estratriene. German OS 24 26 777. 1975 Dec 18.
16. Prezewowsky K, Laurent H, Hofmeister H, Wiechart R, Neumann F, Nishino Y inventors; Schering A.-G., assignee. 1,3-Oxygenated 8α-estratriene. German OS 24 26 778. 1975 Dec 18.
17. Prezewowsky K, Laurent H, Hofmeister H, Wiechert R, Neumann F, Nishino Y inventors; Schering A.-G., assignee. 1,3-Oxygenated 8α-estratriene. German OS 24 26 779. 1975 Dec 18.
18. Howarth NM, Purohit A, Reed MJ, Potter BVL (1994). Estrone sulfamates—potent inhibitors of estrone sulfatase with therapeutic potential. *J Med Chem* **37**:219–221.
19. Li P-K, Rhodes ME, Jagannathan S, Johnson DA (1995). Reversal of scopolamine induced amnesia in rats by the steroid sulfatase inhibitor estrone-3-*O*-sulfamate. *Cognit Brain Res* **2**:251–254
20. Elger W, Schwarz S, Hedden A, Reddersen G, Schneider B (1995).

Sulfamates of various estrogens are prodrugs with increased systemic and reduced hepatic estrogenicity at oral application. *J Steroid Biochem Mol Biol* **55**:395–403.

21. Schwarz S, Elger W (1996). Estrogen sulfamates, a novel approach to oral contraception and hormon replacement therapy. *Drugs Future* **21**:49–61.
22. Schwarz S, Weber G (1975). Steroidsulfamate; Phasentransferkatalysierte Veresterung von Östrogenen mit Sulfonylchloriden. *Z Chem* **15**:270–272.
23. Spillane WJ, Taheny AP, Kearns MM (1982). Versatile synthesis of sulphamate esters by phase-transfer methods. *J Chem Soc Perkin Trans 1* **3**:677–679.
24. Weiß G, Schulze G (1969). Herstellung und Reaktionen von N-Monoalkyl-amidosulfonylchloriden. *Liebigs Ann* **729**:40–51.
25. Atkins GM, Jr., Burgess EM (1967). N-Sulfonylamines. *J Am Chem Soc* **89**:2502–2503.
26. Atkins GM, Jr., Burgess EM (1972). Synthesis and reactions of N-sulfonylamines. *J Am Chem Soc* **94**:6135–6141.
27. Brown HC, Kanner BJ (1966). Preparation and reactions of 2,6-di-*t*-butylpyridine and related hindered bases. A case of steric hindrance toward the proton. *J Am Chem Soc* **88**:986–992.
28. Appel R, Berger G (1958). Hydrazinsulfonsäure-amide. I. Über das Hydrazodisulfamid. *Chem Ber* **91**:1339–1341.
29. Graf R (1959). Umsetzungen mit N-Carbonyl-sulfamidsäue-chlorid. I. Über das Sulfamidsäuechlorid. *Chem Ber* **92**:509–513.
30. Siemann H-J, Droescher P, Undeutsch B, Schwarz S (1995). A novel synthesis of 14α,15α-methylene estradiol (J 824). *Steroids* **60**:308–315.
31. Prousa R, Schönecker B, Tresselt D, Ponsold K (1986). Synthese, Reaktivität und ^{1}H-NMR-Daten von 14,15-Methylenderivaten der Androstan- und Östranreihe. *J Prakt Chem* **328**:55–70.
32. Teichmüller G, Barnikol-Oettler K, Hartmann W inventors; VEB Jenapharm, assignee. Verfahren zur Herstellung von Steroidverbindungen. German Patent DD 74 032. 1968 Jul 9.