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On the Reaction of Some Saccharin Derivatives with Hydrazine and Other Nucleophils

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Summary. The reaction of methyl saccharin-2-acetate with hydrazine gave no 3-hydrazino derivative of saccharin as reported in literature, but yielded with ring opening the benzohydrazide derivative. The analogue reaction was observed when saccharin-2-(2-propionate) was reacted with hydrazine. Furthermore, using an excess of hydrazine, the ester group was transformed into the carbohydrazide too. All hydrazides were fully characterized as hydrazones by reactions with different ketones. The 3-thioxo compounds were prepared by reactions with P_2S_5, but the yield was improved by using *Lawesson*'s reagent. No attack at the ester group was observed. Finally, reactions of the saccharin-2-carboxylate with some amino acids gave substituted benzamides by attack at position 3 and ring opening. In none of the reactions of the saccharin derivatives with nitrogen nucleophiles a formal substitution of the 3-oxo group was observed.

Keywords. Saccharin derivatives; Hydrazine; *Lawesson*'s reagent; Amino acids.

Introduction

3-Oxo-2,3-dihydrobenz[*d*]isothiazole 1,1,dioxide (**1**, saccharin), first prepared by *Remsen* and *Fahlberg* in 1879 [1] is not only used as a sweetener [2]. As a reactive bicyclic system it is intensely modified and transformed [3]. Furthermore, some of its derivatives show interesting pharmacological properties [4]. The reaction of the saccharin derivative **2a** with hydrazine hydrate is described in literature [5], resulting in the replacement of the oxygen in position 3 of the saccharin ring by the hydrazino group. As we could not confirm this reaction, we decided to study the reaction between saccharin derivatives **2a** and **2b** and nucleophils, especially hydrazine hydrate, more in detail.

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Results and Discussion

The derivative **2a** was prepared from saccharin sodium and methyl chloroacetate [6], and the propionate **2b** was obtained by an analogue reaction with methyl (*RS*)-2-chloropropionate [7]. When **2a** was reacted with hydrazine hydrate in EtOH at room temperature as described in [5] we indeed obtained a viscous mass showing a single spot on TLC, which could not be crystallized from any solvent. An analogous result was obtained from **2b**. But, confirmed by all spectral and analytical data, these compounds do not show the structure **3** of a 3-hydrazino saccharin but the benzohydrazide structure **4**. MS spectra show molecular peaks at $m/z = 287$ (**4a**) and 301 (**4b**). The calculated values for structure **3** are 269 and 283.

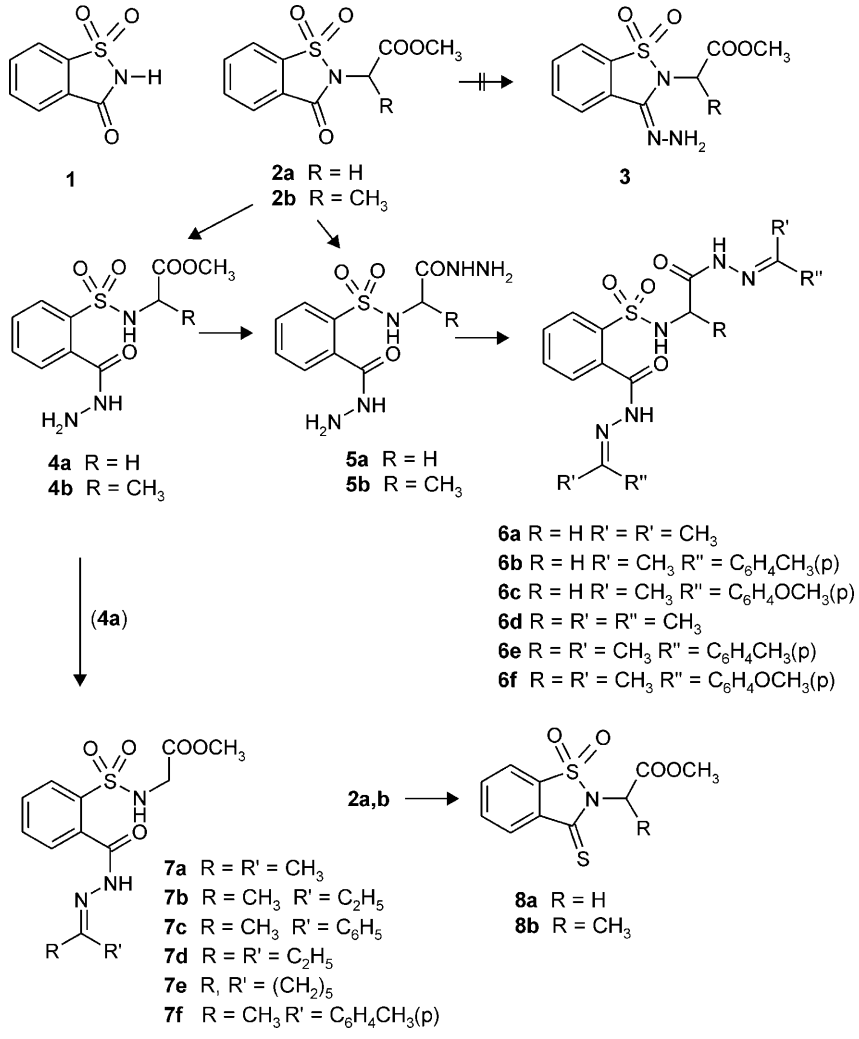
The IR spectra of **2** show carbonyl absorptions around $\bar{\nu} = 1760$ and $1738\,\mathrm{cm}^{-1}$, caused by C=O (position 3) and the ester group, while structures **4** even show two carbonyl absorptions each, one around $\bar{\nu} = 1740\,\mathrm{cm}^{-1}$ from the ester group, and the other around $\bar{\nu} = 1650\,\mathrm{cm}^{-1}$ characterizing the carbohydrazide structure. ^{1}H NMR data and UV spectra support this structure **4**.

Furthermore, when compounds **2** were refluxed with the double amount of hydrazine hydrate in EtOH the bishydrazides **5a** and **5b** were isolated. Identical compounds were obtained from **4a** and **4b** by refluxing with an excess of hydrazine hydrate. The bishydrazone **6** was obtained from the reaction between **5a** and acetone. This reaction clearly supports the structure of **5a**. Analogous results were obtained when we reacted **4a** with a number of ketones. The IR spectra of all isolated compounds **7** show strong carbonyl absorptions of the ester groups at $\bar{\nu} = 1747$–$1753\,\mathrm{cm}^{-1}$, the amide group gives a strong band at $\bar{\nu} = 1651$–$1665\,\mathrm{cm}^{-1}$, and the imine structure (C=N) is detected even by a strong absorption band at $\bar{\nu} = 1630$–$1634\,\mathrm{cm}^{-1}$. ^{1}H NMR spectra and HPLC experiments demonstrate that **7b** and **7c** were obtained as mixtures of (*E*)- and (*Z*)-isomer. From the ^{1}H NMR spectrum of **7c** we deduce a ratio (*Z*) : (*E*) = 1 : 1.3.

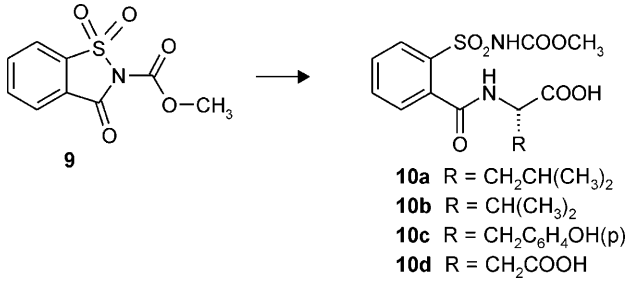
In accordance with Ref. [5] we prepared the thioxo compound **8a** from **2a** by the reaction with phosphorous pentasulfide [8] in 1,4-dioxane. Compound **8b** was obtained by an analogous synthesis, but we found that the transformation into the thioxo compound is much better done and giving higher yields using *Lawesson*'s reagent. Derivatives **8a** and **8b** are nice yellow crystals, and their IR spectra show that only in the saccharin moiety the carbonyl group has reacted with the sulfur reagent. The ester group was not attacked. In the ^{13}C NMR spectrum we find the expected signal of the C=S group at $\delta = 184.6$ ppm, and the signal of the ester carbonyl group at $\delta = 167.9$ ppm.

Finally, we prepared methyl saccharin-2-carboxylate **9** [4], and reacted it with some amino acids in a saturated solution of sodium hydrogen carbonate yielding the *N*-acylated amino acids **10a**–**10d**.

From HPLC experiments with a Chiracel OJ-R column it could be deduced that in all reactions only one defined product was formed and that racemization did not occur. All compounds **10** show an optical rotation in MeOH solution. The IR spectra are characterized by a broad absorption of the carboxylic group $\bar{\nu} > 3000\,\mathrm{cm}^{-1}$, the absorption band of the ester carbonyl group around $\bar{\nu} = 1750\,\mathrm{cm}^{-1}$, the strong amide band at ca. $\bar{\nu} = 1650\,\mathrm{cm}^{-1}$, and the SO_2 bands at ca. $\bar{\nu} = 1355$ and $1170\,\mathrm{cm}^{-1}$, thus confirming the proposed structure.



Scheme 1



Scheme 2

Experimental

General

Melting points: PHMX 80/2778 apparatus (uncorrected); IR spectra (KBr): Perkin-Elmer FTIR 1600; NMR spectra: Bruker DPX 200 (^{1}H: 200 MHz, ^{13}C: 50 MHz), room temperature, internal *TMS*, $CDCl_3$, if not noted otherwise; mass spectra: Intectra AMD 402/3; UV spectra: Uvikon 930, in MeOH; optical rotation: Polartronic D (Schmidt Haensch GmbH); elemental analyses: Perkin-Elmer Elementar Analyzer 2400 CHN: the results agreed with the calculated values within experimental error. TLC: Merck DC-Alufolia, Silica Gel 60 F_{254}, Nr. 5554; HPLC: LaChrom apparatus series 7000 Merck Hitachi; columns: LiChrospher 250-4, RP-18, 5 µm, t_0 (min) with uracil or thiourea, and Chiralcel OJ-R 250-4, 5 µm, t_0 (min) with 1,3,5-tri(*tert*-butyl)benzene: values from RP-18, acetonitrile/water 7:3, if not noted otherwise.

Saccharin sodium was obtained from Merck (Nr. 8.141.14), and *Lawesson*'s Reagent was purchased from Fluka (Nr. 61750). Tetrahydrofuran (*THF*) was stored with $CaCl_2$, then refluxed with Na and benzophenone, and distilled prior to use. Dimethylformamide (*DMF*) was distilled from P_4O_{10} and stored with molecular sieve 4 Å. Other solvents were dried/purified according to literature procedures.

Abbreviations: CC = Column chromatography; *DCC* = Dicyclohexyl Carbodiimide; EtOAc = Ethyl acetate; MeCN = acetonitrile; *NHS* = *N*-Hydroxysuccinimide; *TEA* = Triethylamine; *TFA* = Trifluoroacetic acid.

Methyl 3-Oxo-2,3-dihydrobenzo[d][1,2]thiazol-2-acetate 1,1-Dioxide (**2a**)

See Ref. [6].

Methyl (RS)-2-(3-Oxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)-propionate 1,1-Dioxide (**2b**)

See Ref. [7].

Methyl (2-Hydrazinocarbonylbenzenesulfonylamino)-acetate (**4a**, $C_{10}H_{13}N_3O_5S$)

2a (1.28 g, 5 mmol) was suspended in 10 cm^3 EtOH, and 0.25 g hydrazine hydrate (5 mmol) dissolved in 10 cm^3 EtOH was added dropwise with stirring. When the mixture became clear, the solvent was evaporated *in vacuo*. Yield 0.74 g (51%); IR: $\bar{\nu}$ = 3335, 1569 (NH_2), 1748, 1652 (CO), 1522 (amide II), 1330, 1162 (SO_2) cm^{-1}; ^{1}H NMR (*DMSO-d*$_6$): $\delta = 3.51$ (s, OCH_3), 3.80 (d, CH_2), 4.53 (s, NH_2), 7.47–7.88 (m, 5H, arom. H, NH), 9.80 (s, NH) ppm; UV: $\lambda_{max} = 205$, 269 nm, lg $\varepsilon = 4.31$, 3.34; MS [EI, 70 eV]: $m/z = 287$ (2.08%); HPLC: $k' = 0.34$, $t_0 = 2.52$ (RP-18, acetonitrile/H_2O 1:1).

Methyl (RS)-(2-Hydrazinocarbonylbenzenesulfonylamino)-propionate (**4b**, $C_{11}H_{15}N_3O_5S$)

From **2b** (1.35 g, 5 mmol) as described for **4a**: Yield 0.54 g (38%); IR: $\bar{\nu}$ = 3335, 1570 (NH_2), 1742, 1651 (CO), 1524 (amide II), 1337, 1159 (SO_2) cm^{-1}; ^{1}H NMR (*DMSO-d*$_6$): $\delta = 1.18$ (d, CH_3), 3.33 (s, OCH_3), 4.05 (m, CH), 4.54 (s, NH_2), 7.48–7.89 (m, 5H, arom. H, NH), 9.83 (s, NH) ppm; UV: $\lambda_{max} = 206$, 281 nm, lg $\varepsilon = 4.40$, 3.31; MS [EI, 70 eV): $m/z = 301$ (1.9%); HPLC: $k' = 0.44$, $t_0 = 2.52$ (RP-18, acetonitrile/H_2O 1:1).

2-(Hydrazinocarbonylmethylsulfamoyl)-benzohydrazide (**5a**, $C_9H_{13}N_5O_4S$)

a) From **2a** (1.28 g, 5 mmol) and 0.5 g hydrazine hydrate (10 mmol) in 12 cm^3 EtOH by refluxing for 2 h. After cooling to room temp., the precipitate was separated. b) From **4a** (0.5 g, 1.7 mmol) and 0.09 g hydrazine hydrate (1.7 mmol) in 2.5 cm^3 EtOH as a): Yield: a) 0.8 g (54%), b) 0.2 g (14%); colorless crystals; mp 139–143°C (MeOH); IR: $\bar{\nu}$ = 3336, 1590 (NH_2), 1670, 1615 (CO), 1517 (amide II),

1338, 1159 (SO_2) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 3.45$ (s, CH_2), 4.14 (d, NH_2), 4.56 (d, NH_2), 7.35 (s, NH), 7.50–7.88 (m, 4H, arom. H), 9.12 (s, NH), 9.89 (s, NH) ppm; UV: $\lambda_{max} = 205$, 269 nm, lg $\varepsilon = 4.33$, 3.34; MS [EI, 70 eV]: $m/z = 255$ [M^+–NH–NH_2] (11.01%); HPLC: $k' = 0.17$, $t_0 = 2.00$ (RP-18, acetonitrile/H_2O 7:3).

2-(Hydrazinocarbonylethylsulfamoyl)-benzohydrazide (**5b**, $C_{10}H_{15}N_5O_4S$)

a) From **2b** (1.35 g, 5 mmol) or b) from **4b** (0.36 g, 1.2 mmol) as **5a**: Yield: a) 1.0 g (60%), b) 0.06 g (16%); colorless crystals; mp 185°C (MeOH); IR: $\bar{\nu} =$ 3317, 1590 (NH_2), 1627, 1648 (CO), 1519 (amide II), 1333, 1169 (SO_2) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 1.06$ (d, CH_3), 3.81 (m, CH), 4.07 (d, NH_2), 4.57 (d, NH_2), 7.35–7.45 (s, NH), 7.48–7.89 (m, 4H, arom. H), 9.16 (s, NH), 9.90 (s, NH) ppm; ^{13}C NMR (*DMSO-d_6*): $\delta = 19.4$ (CH_3), 51.0 (CH), 128.2, 129.7, 130.3, 132.8, 133.9, 138.5 (arom. C), 167.3, 170.2 (CO) ppm; UV: $\lambda_{max} = 205$, 268 nm, lg $\varepsilon = 4.34$, 3.35; MS [EI, 70 eV]: $m/z = 301$ (6.32%); HPLC: $k' = 0.25$, $t_0 = 2.00$ (RP-18, acetonitrile/H_2O 7:3).

N′-Isopropylidene-2-[(N′-isopropylidenehydrazinocarbonylmethyl)-sulfamoyl]-benzohydrazide (**6a**, $C_{15}H_{21}N_5O_4S$)

Compound **5a** (1.44 g, 5 mmol) and 1.8 g acetone (20 mmol) were refluxed for 1 h in 10 cm^3 EtOH, and then stirred at room temperature for 1 h: Yield 0.76 g (42%); colorless crystals; mp 180–182°C (EtOH); IR: $\bar{\nu} =$ 3319, 1539 (NH), 1712 (CO), 1658 (C=N), 1338, 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.51$ (m, 4 CH_3), 3.91 (m, CH_2), 6.60 (s, NH), 7.52–7.95 (m, 4H, arom. H), 8.28 (s, NH), 9.22 (s, NH) ppm; HPLC: $k' = 0.13$, $t_0 = 1.77$ (RP-18, acetonitrile/H_2O 7:3).

N′-(α,4-Dimethylbenzylidene)-2-{N-[N′-(α,4-dimethylbenzylidene)-hydrazinocarbonylmethyl]-sulfamoyl}-benzohydrazide (**6b**, $C_{27}H_{29}N_5O_4S$)

From **5a** and 4-methylacetophenone analogous to **6a**: Yield 1.80 g (69%); colorless crystals; mp 207–212°C (EtOH).

N′-(4-Methoxy-α-methylbenzylidene)-2-{N-[N′-(4-methoxy-α-methylbenzylidene)-hydrazinocarbonylmethyl]-sulfamoyl}-benzohydrazide (**6c**, $C_{27}H_{29}N_5O_6S$)

From **5a** and 4-methoxyacetophenone analogous to **6a**: Yield 1.94 g (70%); colorless crystals; mp 182–186°C (EtOH).

(RS)-N′-Isopropylidene-2-{[1-(isopropylidenehydrazinocarbonyl)-1-ethyl]-sulfamoyl}-benzohydrazide (**6d**, $C_{16}H_{23}N_5O_4S$)

From **5b** and acetone analogous to **6a**: Yield 1.20 g (63%); colorless crystals; mp 212–214°C (EtOH).

(RS)-N′-(α,4-Dimethylbenzylidene)-2-{[1-(α,4-dimethylbenzylidenehydrazinocarbonyl)-1-ethyl]-sulfamoyl}-benzohydrazide (**6e**, $C_{28}H_{31}N_5O_4S$)

From **5b** and 4-methylacetophenone analogous to **6a**: Yield 1.50 g (56%); colorless crystals; mp 185–188°C (EtOH).

(RS)-N′-(4-Methoxy-α-methylbenzylidene)-2-{[1-(4-methoxy-α-methylbenzylidenehydrazinocarbonyl)-1-ethyl]-sulfamoyl}-benzohydrazide (**6f**, $C_{28}H_{31}N_5O_6S$)

From **5b** and 4-methoxyacetophenone analogous to **6a**: Yield 2.04 g (72%); colorless crystals; mp 204–208°C (EtOH).

Synthesis of **7** (*General Procedure*)

Compound **4a** (1.43 g, 5 mmol) and 10 mmol ketone dissolved in 15 cm^3 EtOH were refluxed for 1 h. After cooling to room temperature for 12 h, the solution was evaporated *in vacuo*, and a few drops of EtOH were added to the residue. The colorless crystals were recrystallized from EtOH.

Methyl [2-(Isopropylidenehydrazinocarbonyl)-benzenesulfonylamino]-acetate (**7a**, $C_{13}H_{17}N_3O_5S$)

From acetone: Yield 1.36 g (85%); mp 184–185°C; IR: $\bar{\nu} = 3221$, 1547 (NH), 1747, 1651 (CO, amide), 1632 (C=N), 1359, 1173 $(SO_2)\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.99$ (s, CH_3), 2.15 (s, CH_3), 3.58 (s, OCH_3), 3.77 (d, CH_2), 6.60 (s, NH), 7.53–7.77 (m, 4H, arom. H), 9.05 (s, NH) ppm; HPLC: $k' = 0.25$, $t_0 = 2.53$ (RP-18, acetonitrile/H_2O 7:3).

Methyl (E/Z)-[2-(1-Methylpropylidenehydrazinocarbonyl)-benzenesulfonylamino]-acetate (**7b**, $C_{14}H_{19}N_3O_5S$)

From ethyl methyl ketone: Yield 0.77 g (46%); colorless crystals; mp 155°C.

Methyl (E/Z)-[2-(α-Methylbenzylidenehydrazinocarbonyl)-benzenesulfonylamino]-acetate (**7c**, $C_{18}H_{19}N_3O_5S$)

From acetophenone: Yield 1.1 g (57%); colorless crystals; mp 158°C.

Methyl [2-(1-Ethylpropylidenehydrazinocarbonyl)-benzenesulfonylamino]-acetate (**7d**, $C_{15}H_{21}N_3O_5S$)

From diethyl ketone: Yield 0.9 g (51%); colorless crystals; mp 113°C.

Methyl [2-(Cyclohexylidenehydrazinocarbonyl)-benzenesulfonylamino]-acetate (**7e**, $C_{16}H_{21}N_3O_5S$)

From cyclohexanone: Yield 1.32 g (73%); colorless crystals; mp 170°C.

Methyl [2-(α,4-Dimethylbenzylidenehydrazinocarbonyl)-benzenesulfonylamino]-acetate (**7f**, $C_{19}H_{21}N_3O_5S$)

From 4-methylacetophenone: Yield 1.35 g (67%); colorless crystals; mp 165–168°C.

Methyl 3-Thioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-acetate 1,1-dioxide (**8a**, $C_{10}H_9NO_4S_2$)

From **2a** (1.02 g, 4 mmol) and 1.18 g P_2S_5 (8 mmol) as described in [5]: Yield 0.8 g (74%); yellow crystals; mp 128–130°C (EtOH; Ref. [5]: 114–115°C); IR: $\bar{\nu} = 3084$–2956 (CH), 1760 (*CO*), 1458 (*CS*), 1308, 1182 $(SO_2)\,cm^{-1}$; ^1H NMR (*DMSO-d_6*): $\delta = 3.70$ (s, OCH_3), 4.95 (s, CH_2), 8.03–8.38 (m, 4H, arom. H) ppm; HPLC: $k' = 2.94$, $t_0 = 2.71$ (RP-18, acetonitrile/0.002 m KH_2PO_4, *pH* = 6.57, 1:1).

Methyl (RS)-2-(3-Thioxo-2,3-dihydrobenzo[d][1,2]thiazol-2-yl)-propionate 1,1-dioxide (**8b**, $C_{11}H_{11}NO_4S_2$)

a) From **2b** (1.08 g, 4 mmol) and 1.76 g P_2S_5 (8 mmol) according to **8a**. b) From **2b** (1.08 g, 4 mol) and 0.81 g *Lawesson*'s reagent (2 mmol) by stirring and refluxing in 10 cm^3 dioxane for 2 h. Workup as a):

Yield: a) 0.85 g (75%); b) 1.02 g (90%); yellow crystals; mp 153°C (EtOH); IR: $\bar{\nu} = 3088-3004$ (CH), 1742 (CO), 1454 (CS), 1299, 1189 (SO_2) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 1.75$ (d, CH_3), 3.64 (s, OCH_3), 5.53 (q, CH), 7.98–8.35 (m, 4H, arom. H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.7$ (CH_3), 51.7 (CH), 52.6 (OCH_3), 121.6, 126.4, 128.9, 135.6 (arom C), 167.9 (CO), 184.6 (CS); HPLC: $k' = 6.12$, $t_0 = 2.52$ (RP-18, acetonitrile/H_2O 1:1).

Methyl 3-Oxo-2,3-dihydrobenzo[d][1,2]thiazol-2-carboxylate 1,1-dioxide (**9**)

See Ref. [4].

Synthesis of **10** (*General Procedure*)

With stirring, the amino acid and an equimolar amount of **9** were dissolved in 15 cm^3 satd. solution of $NaHCO_3$, cooled to 0°C, and 29 cm^3 *THF* was added. The mixture was stirred at 40°C for 2 h, and then adjusted with sulfuric acid to *pH* = 6–7, concentrated *in vacuo* to half of the volume, and acidified to *pH* = 1–2. Then it was extracted with EtOAc, the organic layer was washed with a satd. solution of NaCl, dried (Na_2SO_4), and evaporated. The residue was purified from excess of **9** by extraction with diethyl ether (Soxhlet).

N-[2-(N-Methoxycarbonylsulfamoyl)-benzoyl]-L-leucine (**10a**, $C_{15}H_{20}N_2O_7S$)

From L-leucine (0.38 g, 2.9 mmol): Yield 0.93 g (89%); colorless crystals; mp 75–78°C; $[\alpha]_D^{20} = +17.8$ ($c = 2$, MeOH); IR: $\bar{\nu} = 3359$, 1539 (NH), 2961 (CH), 1749, 1651 (CO, amide), 1357, 1165 (SO_2) cm^{-1}; ^1H NMR (*MeOH-d_4*): $\delta = 0.97$ (d, $J = 6.2$ Hz, CH_3), 1.00 (d, $J = 6.3$ Hz, CH_3), 1.66–1.82 (m, 3H, $CHCH_2$), 3.64 (s, OCH_3), 4.65 (t, $J = 7.3$ Hz, CH), 7.60–8.11 (m, 4H, arom. H) ppm; HPLC: $k' = 0.79$, $t_0 = 1.75$ (RP-18, acetonitrile/50 mmol KH_2PO_4, *pH* = 3.6; 1:1); $k' = 1.15$, $t_0 = 2.13$ (Chiralcel OJ-R, acetonitrile/50 mmol KH_2PO_4, *pH* = 3.33; 15:85).

N-[2-(N-Methoxycarbonylsulfamoyl)-benzoyl]-L-valine (**10b**, $C_{14}H_{18}N_2O_7S$)

From L-valine (0.34 g, 2.9 mmol): Yield 0.93 g (92%); colorless crystals; mp 141–145°C; $[\alpha]_D^{20} = +30.0$ ($c = 2$, MeOH); IR: $\bar{\nu} = 3343$, 1540 (NH), 2971–2884 (CH), 1736, 1716 (CO), 1651 (CO amide), 1359, 1171 (SO_2) cm^{-1}; ^1H NMR (*DMSO-d_6*): $\delta = 0.94$ (d, $J = 6.7$ Hz, CH_3), 0.96 (d, $J = 6.7$ Hz, CH_3), 1.98 (m, CH), 3.56 (s, OCH_3). 4.35 (dd, $J = 7.3$ Hz, CH), 7.47–8.04 (m, 4H, arom. H), 8.66 (d, NH) ppm; HPLC: $k' = 0.50$, $t_0 = 1.75$ (RP-18, acetonitrile/50 mmol KH_2PO_4, *pH* = 3.6; 1:1); $k' = 0.54$, $t_0 = 2.13$ (Chiralcel OJ–R, acetonitrile/50 mmol KH_2PO_4, *pH* = 3.33; 15:85).

N-[2-(N-Methoxycarbonylsulfamoyl)-benzoyl]-L-tyrosine (**10c**, $C_{18}H_{20}N_2O_9S$)

From L-tyrosine (0.37 g, 2.0 mmol): Yield 0.7 g (80%); viscous solid; $[\alpha]_D^{20} = +20.2$ ($c = 2$, MeOH); IR: $\bar{\nu} = 3290$, 1516 (NH), 3290–2875 (OH), 1732, 1650 (CO, amide), 1354, 1163 (SO_2) cm^{-1}; ^1H NMR (*MeOH-d_4*): $\delta = 2.91-3.31$ (m, CH_2), 3.64 (s, OCH_3), 4.08 (q, $J = 7.2$ Hz, CH), 6.70–7.32, 7.59–8.13 (2 m, each 4H, arom. H) ppm; HPLC: $k' = 0.30$, $t_0 = 1.75$ (RP-18, acetonitrile/50 mmol KH_2PO_4, *pH* = 3.6; 1:1); $k' = 0.59$, $t_0 = 2.13$ (Chiralcel OJ–R, acetonitrile/50 mmol KH_2PO_4, *pH* = 3.33; 15:85).

N-[2-(N-Methoxycarbonylsulfamoyl)benzoyl]-L-aspartic acid (**10d**, $C_{13}H_{14}N_2O_9S$)

From L-aspartic acid (0.77 g, 5.8 mmol): Yield 1.3 g (60%); viscous solid; $[\alpha]_D^{20} = +10.3$ ($c = 2$, MeOH); IR: $\bar{\nu} = 3351$, 1540 (NH), 3351–2880 (OH), 1736, 1648 (CO, amide), 1355, 1163

(SO_2) cm^{-1}; ^1H NMR (*MeOH-d_4*): $\delta = 2.97$ (dd, $J = 2.2$, 2.7 Hz, CH_2), 3.64 (s, OCH_3), 4.09 (q, $J = 7.1$ Hz, CH), 7.59–8.11 (m, 4H, arom. H) ppm; HPLC: $k' = 0.01$, $t_0 = 2.45$ (RP-18, acetonitrile/50 mmol KH_2PO_4, $pH = 3.6$; 1:1); $k' = 0.02$, $t_0 = 2.61$ (Chiralcel OJ–R, acetonitrile/50 mmol KH_2PO_4, $pH = 3.33$; 15:85).

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