The Synthesis of 3,4-Dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acids

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Dedicated to Professor Aleš Krbavčič, Ljubljana, on the occasion of his 60th birthday

The synthesis of 3,4-dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic acids **4a,b**, **6a-e** is presented. After the condensation of *o*-aminothiophenols with diethyl 2-bromo-2-methylmalonate in the presence of KF as a catalyst the nitrogen in the fused derivatives **3a,b**, was alkylated to provide **5a-f**, the corresponding esters **3a,b**, **5a-f** were hydrolysed.

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The 1,4-benzothiazine moiety can be found in molecules, which have been tested on Aldose Reductase inhibition [1], Ca^{2+} antagonism [2], immunomodulating properties [3], antagonism of α_2-adrenoreceptors [4] and anti-inflamatory activity [5].

Synthetic routes for the preparation of 3,4-dihydro-3-oxo-2*H*-benzo-1,4-thiazines and 3,4-dihydro-3-oxo-2*H*-benzo-1,4-oxazines have been reported [1,3,5,6,7,8,9]. The corresponding *o*-aminothiophenols undergo reaction with different nucleofiles (*e.g.*, diethyl fumarate [1], diethyl 2-halomalonate [3], chloroacetic acid [5] were used as the reagents). According to our knowledge, there is no reference describing the synthesis of 2-alkyl derivatives of 3,4-dihydro-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic acids.

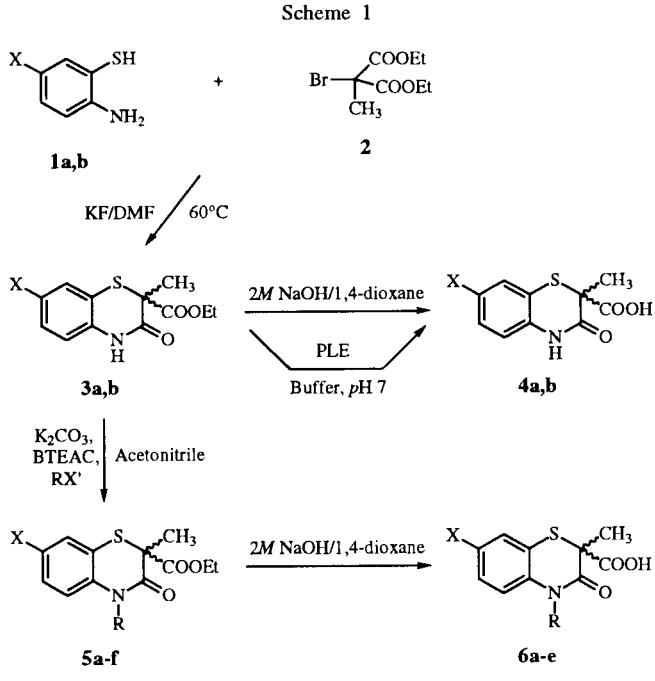
Ethyl 3,4-dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylates **3a**, **3b** were synthesized from *o*-aminothiophenols and diethyl 2-bromo-2-methylmalonate. Reactions catalyzed with KF provided higher yields than those without a catalyst. An argon atmosphere was necessary because *o*-aminothiophenols had the tendency to form disulfides in the presence of oxygen. During the isolation the mixture of **3a**, **3b** in cold water should not contain ethyl 2-bromo-2-methylmalonate in order to avoid the difficulties in precipitating of the product.

N-Alkylating reactions on compounds **5a-5f** were performed using phase transfer catalysis [10-13]. Benzyl triethylammonium chloride (BTEAC) was used as a catalyst, potassium carbonate as a base and an alkyl halide as the alkylating reagent. The non-aqueous media was not imperative for the reactions. Yields were higher (20-30%) and the purity of products was better in comparison to the products isolated after *N*-alkylation using classical reaction conditions (NaH, anhydrous toluene, alkyl halide).

The hydrolysis of the esters **3a**, **3b** and **5a-5f** with sodium hydroxide in 1,4-dioxane gave corresponding acids **4a**, **4b** and **6a-6e** in good yields. We also used enzyme hydrolysis [14-16], catalyzed by PLE (Pig Liver Esterase) which gave the acids with no or minimal optical rotation. The enzyme hydrolysis was not stereoselective.

The kinetic resolution of enantiomers gave the optically active products (+) and (-)-3,4-dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic acids **7a**, **7b** and (-) and (+)-3,4-dihydro-4-ethyl-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic acid **8a**, **8b**. Because of the different solubility of compounds **4a** and **6b** in ethanol, after the kinetic resolution using *S*(-)-phenylethylamine, different enantiomers were isolated, compound **7a** with optical rotation of +12.67° and compound **8a** with optical rotaton of-15,14°. Due to hygroscopic nature of synthesized compounds, the C H N analyses may differ more then 0.4% in some cases. The structure of the products synthesized was elucidated by ^{1}H nmr spectroscopy.

Scheme 1



Compound	X	R	RX'
3a	H	—	—
3b	Cl	—	—
4a	H	—	—
4b	Cl	—	—
5a	H	Me	MeI
5b	H	Et	EtBr
5c	H	Pr	PrBr
5d	H	Bz	BzBr
5e	Cl	Me	MeI
5f	Cl	*i*-Pr	*i*-PrBr

Compound	X	R
6a	H	Me
6b	H	Et
6c	H	Pr
6d	H	Bz
6e	Cl	Me

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. The ir spectra were recorded on a Perkin Elmer FTIR 1600 spectrophotometer. The ^{1}H nmr spectra were measured on a Varian VXR 300 at 300 MHz, using TMS as internal standard. Elementary analyses were performed on a Perkin Elmer 240 C, C H N analyzer. Mass spectra were obtained using AUTOSPEC Q (VG analytical) mass spectrometer. The enzyme reactions were performed by using Methrom: dosimat 725, inpulsomat 614, *p*H meter 691.

Synthesis of Ethyl 3,4-Dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylates.

General Procedure.

Ethyl 3,4-Dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**3a**).

To a stirred suspension of potassium fluoride (3.00 g, 0.052 mole) in anhydrous DMF (14 ml) under argon atmosphere, diethyl 2-bromo-2-methylmalonate (**2**) (5.15 g, 0.020 mole) was added. After 15 minutes 2-aminothiophenol (**1a**) (2.50 g, 0.020 mole) was added. The mixture was stirred for 15 minutes at room temperature, than at 60° for 6 hours, cooled to room temperature and stirred for another 18 hours at this temperature. The mixture was poured into ice/water (80 g). The precipitate was filtered off, washed with cold water and recrystallized from ethanol to yield 3.80 g (76%) of **3a**, mp 110-111°; ir (potassium bromide): ν 3448 (NH), 1743 (COOEt), 1665 (CONH), 1588, 1484, 1381, 1238, 1119, 1010, 932, 858, 826, 747, 709, 681 cm^{-1}; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 1.00 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.80 (s, 3H, CH_3); 3.95-4.40 (m, 2H, CH_2), 6.85-7.35 (ABX_3-m, 4H, phenyl), 8.85 (s, 1H, NH) ppm.

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.37; H, 5.18; N, 5.58. Found: C, 57.52; H, 4.89; N, 5.58.

Ethyl 7-Chloro-3,4-dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**3b**).

In a similar manner **3b** was prepared from potassium fluoride (3.0 g, 0.052 mole), diethyl 2-bromo-2-methylmalonate (**2**) (5.15 g, 0.020 mole) and 2-amino-5-chlorothiophenol [17] (**1b**) (3.20 g, 0.020 mole). The 2-amino-5-chlorothiophenol [17] was synthesized in better yields by the modified method, using *p*-chloroaniline, cupric chloride hydrate and molecular sieves (4Å). Recrystallization of the crude product from ethanol afforded white powder of **3b**, yield 4.00 g (70%), mp 159-161°; ir (potassium bromide): ν 3445 (NH), 2976 (CH), 1736 (COOEt), 1666 (CONH), 1472, 1231, 1102, 837 cm^{-1}; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 1.05 (t, 3H, J = 7.1 Hz, CH_2CH_3); 1.80 (s, 3H, CH_3), 4.00-4.20 (m, 2H, CH_2), 6.90 (d, 1H, $J_{5,6}$ = 8.5 Hz, H_5), 7.17 (dd, 1H, $J_{5,6}$ = 8.5 Hz, $J_{6,8}$ = 2.2 Hz, H_6), 7.29 (d, 1H, $J_{5,6}$ = 2.4 Hz, H_8), 9.35 (s, 1H, NH) ppm; ms: EI+ (M^+, 285) 285 (40), 212 (100), 184 (31), 143 (5), 83 (5), 69 (6).

The Synthesis of *N*-Alkylated-benzo-1,4-thiazines.

General Procedure.

Ethyl 3,4-Dihydro-2,4-dimethyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**5a**).

To the mixture of ethyl 3,4-dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**3a**) (1.01 g, 4 mmoles), potassium carbonate (1.18 g, 8.5 mmoles) and BTEAC (0.45 g, 2 mmoles) in 20 ml acetonitrile, iodomethane (1.42 g, 10 mmoles) was added. After the addition was completed, the stirring was continued for 20 hours at the reflux temperature. The precipitate was filtered off, the solvent was evaporated *in vacuo* and the residue dissolved in toluene, washed with 60 ml of 0.1 *M* sodium hydroxide and with 40 ml of a saturated solution of sodium chloride. The organic phase was dried over magnesium sulfate, filtered off and evaporated *in vacuo* to yield 0.88 g (83%) of **5a** as a yellow oil; ir (sodium chloride film): ν 2983 (NH), 1726 (COOEt), 1670 (CONH), 1587, 1479, 1353, 1250, 1111, 755, cm^{-1}; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 0.94 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.78 (s, 3H, CH_3), 3.50 (s, 3H, N-CH_3), 3.88-4.10 (m, 2H, CH_2), 6.99-7.39 (m, 4H, phenyl) ppm.

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.86; H, 5.66; N, 5.28. Found: C, 58.70; H, 5.45; N, 5.19.

Ethyl 3,4-Dihydro-4-ethyl-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**5b**).

Compound **5b** was obtained in a similar manner from ethyl 3,4-dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**3a**) (1.01 g, 4 mmoles), potassium carbonate (1.18 g, 8.5 mmoles) and BTEAC (0.45 g, 2 mmoles), 20 ml acetonitrile and bromoethane (1.09 g, 10 mmoles), yield 0.95 g (85%); ir (sodium chloride film): ν 3066 (NH), 2980, 2872 (CH), 1910, 1731 (COOEt), 1666 (CONH), 1480, 1377, 1255 cm^{-1}; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 0.96 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.35 (t, 3H, J = 7.1 Hz, N-CH_2CH_3), 1.77 (s, 3H, CH_3), 3.79-4.40 (m, 4H, 2 x CH_2CH_3), 6.90-7.40 (m, 4H, phenyl) ppm.

Anal. Calcd. for $C_{14}H_{17}NO_3S$: C, 60.22; H, 6.09; N, 5.02. Found: C, 59.82; H, 5.71; N, 4.49.

Ethyl 3,4-Dihydro-2-methyl-3-oxo-4-propyl-2*H*-benzo-1,4-thiazine-2-carboxylate (**5c**).

From ethyl 3,4-dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**3a**) (1.01 g, 4 mmoles), potassium carbonate (1.18 g, 8.5 mmoles), BTEAC (0.45 g, 2 mmoles), 20 ml acetonitrile and *n*-propyl bromide (1.22 g, 10 mmoles), **5c** was obtained in a yield of 0.77 g (66%); ir (sodium chloride film): ν 2965 (NH), 1738 (COOEt), 1682 (CONH), 1586, 1480, 1446, 1372, 1258, 1114, 1017, 752 cm^{-1}; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 0.96 (t, 3H, J = 7.1 Hz, CH_2CH_3), 0.98 (t, 3H, J = 7.6 Hz, $CH_2CH_2CH_3$), 1.64-1.74 (m, 2H, $CH_2CH_2CH_3$), 1.77 (s, 3H, CH_3), 3.80-4.14 (m, 4H, $CH_2CH_2CH_3$, CH_2CH_3), 6.98-7.38 (m, 4H, phenyl) ppm; ms: EI+ (M+ 293), 293 (51), 220 (100), 192 (42), 178 (22), 162 (5), 150 (28), 136 (9), 109 (13).

Anal. Calcd. for $C_{15}H_{19}NO_3S$: C, 61.43; H, 6.48; N, 4.78. Found: C, 60.93; H, 6.44; N, 4.76.

Ethyl 3,4-Dihydro-4-benzyl-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**5d**).

Compound **5d** was obtained from ethyl 3,4 dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**3a**) (1.01 g, 4 mmoles), potassium carbonate (1.18 g, 8.5 mmoles), BTEAC (0.45 g, 2 mmoles), 20 ml acetonitrile and benzyl bromide (1.71 g, 10 mmoles) in a yield of 0.70 g (51%); ir (sodium chloride film): ν 3064 (NH), 2981 (CH), 1743 (COOEt), 1673 (CONH), 1479, 1448, 1376, 1263, 1113 cm^{-1}; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 0.93 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.71 (s, 3H, CH_3), 3.90-4.10 (m, 2H, CH_2CH_3), 5.16 (s, 2H, CH_2Ph), 7.00-7.60 (m, 9H, aromatic H) ppm.

Anal. Calcd. for $C_{19}H_{19}NO_3S$: C, 66.86; H, 5.57; N, 4.10. Found: C, 66.49; H, 5.18; N, 3.88.

Ethyl 3,4-Dihydro-7-chloro-2,4-dimethyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**5e**).

Compound **5e** was prepared from ethyl 3,4-dihydro-7-chloro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**3b**) (1.14 g, 4 mmoles), potassium carbonate (1.18 g, 8.5 mmoles), BTEAC (0.45 g, 2 mmoles), 20 ml acetonitrile and methyl iodide (1.42 g, 10 mmoles), yield 0.38 g (32%); ir (sodium chloride film): ν 2981 (NH), 2935, 2860 (CH), 1738 (COOEt), 1635 (CONH), 1479, 1345, 1250, 1106, 1012, 868, 813 cm^{-1}; ^1H nmr (deuteriochloroform, 300 MHz): δ 1.00 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.78 (s, 3H, CH_3), 3.45 (s, 3H, N-CH_3), 3.93-4.15 (m, 2H, CH_2CH_3), 6.95-7.40 (m, 3H, Ph) ppm. The CHN analysis for the acid **6e** prepared from **5e** was correct.

Ethyl 3,4-Dihydro-7-chloro-4-isopropyl-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**5f**) and Ethyl 3,4-Dihydro-7-chloro-3-isopropyloxy-2-methyl-2*H*-benzo-1,4-thiazine-2-carboxylate.

From ethyl 3,4-dihydro-7-chloro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylate (**3b**) (1.14 g, 4 mmoles), potassium carbonate (1.18 g, 8.5 mmoles), BTEAC (0.45 g, 2 mmoles), 20 ml acetonitrile and *i*-propyl bromide (1.22 g, 10 mmoles), the product yield was 0.53 g (41%); ir (sodium chloride film): ν 2979 (NH), 2936, 2871 (CH), 1742 (COOEt), 1681 (CONH), 1633, 1475, 1474, 1254, 1106, 1017, 814 cm^{-1}; ^1H nmr (deuteriochloroform, 300 MHz): δ 0.95 (t, 3H, J = 7.1 Hz, from *N*-alkylated product, CH_2CH_3), 1.17 (t, 3H, J = 7.2 Hz, from *O*-alkylated product, CH_2CH_3), 1.49 (d, 3H, J = 6.8 Hz, CH_3CH-N), 1.58 (d, 3H, J = 6.8 Hz, CH_3CH-O), 1.68 (s, 3H, from *N*-alkylated product, CH_3), 1.77 (s, 3H, from *O*-alkylated product, CH_3), 3.85-4.05 (m, 2H, from *N*-alkylated product, CH_2CH_3), 4.05-4.20 (m, 2H, from *O*-alkylated product, CH_2CH_3), 4.55-4.75 (m, 1H, N-$CH(CH_3)_2$), 5.30-5.50 (m, 1H, O-$CH(CH_3)_2$), 7.05-7.42 (m, 3H, Ph) ppm. The ratio between *N*-and *O*-alkylating product was 1:7 according to the nmr spectra. The *N*- and *O*-alkylating products were not separated.

Anal. Calcd. for $C_{19}H_{19}NO_3S$: C, 54.95; H, 5.53; N, 4.27. Found: C, 55.38; H, 5.71; N, 4.11.

The Synthesis of 3,4-Dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acids.

General Procedure A.

3,4-Dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**4a**).

A solution of **3a** (0.25 g, 1 mmole) and 2*M* sodium hydroxide (1 ml) in 1,4-dioxane (5 ml) was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure. The residue was dissolved in water and acidified to *p*H 2 with 2*M* hydrochloric acid. The precipitate was filtered off and washed with ethanol to give 0.21 g (94%) white crystals of **4a**, mp 164-165°; ir (potassium bromide): ν 3448 (NH), 1743 (COOH), 1665 (CONH), 1588, 1484, 1381, 1238, 1119, 1010, 932, 858, 826, 747, 709, 681 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.60 (s, 3H, CH_3), 6.95-7.35 (ABX_3 m, 4H, phenyl), 10.80 (s, 1H, NH) ppm.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.81; H, 4.04; N, 6.28. Found: C, 54.41; H, 3.47; N 5.70.

3,4-Dihydro-7-chloro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**4b**).

Compound **4b** was obtained from **3b** (0.29 g, 1 mmole), 2*M* sodium hydroxide (1 ml) in 1,4-dioxane (5 ml) as white crystals, yield 0.16 g (60%), mp 156-157°; ir (potassium bromide): ν 3195 (NH, 2258 (COOH), 1702 (COOH), 1676 (CONH), 1481, 1375, 1281, 1073, 917, 827, 632 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.60 (s, 3H, CH_3), 7.01 (d, 1EI, $J_{5,6}$ = 8.8 Hz, H_5), 7.27 (dd, 1H, $J_{5,6}$ = 8.5 Hz, $J_{6,8}$ = 2.4 Hz, H_6), 7.46 (d, 1H, $J_{6,8}$ = 2.2 Hz, H_8) ppm.

Anal. Calcd. for $C_{10}H_8ClNO_3S$: C, 46.60; H, 3.10; N, 5.44. Found: C, 46.33; H, 3.29; N, 5.21.

3,4-Dihydro-2,4-dimethyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**6a**).

This compound was obtained from **5a** (0.27 g, 1 mmole), 2*M* sodium hydroxide (1 ml) in 1,4-dioxane (5 ml) as white crystals, yield 0.21 g (90%), mp 141-146°; ir (potassium bromide): ν 3564 (NH), 1711 (COOH), 1651 (CONH), 1586, 1456, 1374, 1246, 1169 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.45 (s, 3H, CH_3), 3.31 (s, 3H, N-CH_3), 6.85-7.25 (m, 4H, phenyl) ppm.

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.69; H, 4.64; N, 5.90. Found: C, 55.45; H, 4.54; N, 6.01.

3,4-Dihydro-4-ethyl-2-methyl-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**6b**).

This compound was obtained from **5b** (0.28 g, 1 mmole), 2*M* sodium hydroxide (1 ml) in 1,4-dioxane (5 ml) as a white powder, yield 0.21 g (87%), mp 122-125°; ir (potassium bromide): ν 3479 (NH), 2982 (COOH), 1724 (COOH), 1658 (CONH), 1576, 1448, 1266, 1233, 1115 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.17 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.61 (s, 3H, CH_3), 3.80-4.01 and 4.01-4.20 (2m, 1H each, CH_2CH_3), 7.00-7.50 (m, 4H, phenyl) ppm.

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.37; H, 5.18; N, 5.57. Found: C, 57.55; H, 5.30; N, 5.60.

3,4-Dihydro-2-methyl-3-oxo-4-propyl-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**6c**).

This compound was obtained from **5c** (0.29 g, 1 mmole), 2*M* sodium hydroxide (1 ml) in 1,4-dioxane (5 ml) as a viscose oil, yield 0.16 g (59%), ir (potassium bromide): ν 2962 (NH, COOH), 1732 (COOH), 1654 (CONH), 1586, 1450, 1384, 1263, 1118, 1046, 876, 755 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 0.84 (t, 3H, J = 7.3 Hz, CH_3), 1.60 (s, 3H, CH_3), 3.90-4.00 (m, 4H, 2 x CH_2), 7.00-7.40 (m, 4H, Ph) ppm.

Anal. Calcd. for $C_{13}H_{15}NO_3S \cdot 1/4H_2O$: C, 57.88; H, 5.75; N, 5.19. Found: C, 58.30; H, 6.27; N, 5.25.

3,4-Dihydro-4-benzyl-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**6d**).

This compound was obtained from **5d** (0.34 g, 1 mmole), 2*M* sodium hydroxide (1 ml) in 1,4-dioxane (5 ml) as a viscose oil, yield 0.10 g (30%), ir (sodium chloride film): ν 3450, 1726, 1655, 1570, 1450, 1390, 1265, 1167, 735, 693 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.66 (s, 3H, CH_3), 5.07 (d, 1H, AB system, J = 16.6 Hz, CH_2Ph), 5.38 (d, 1H, AB system, J = 16.6 Hz, CH_2Ph), 7.01-7.41 (m, 9H, aromatic H) ppm.

Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.17; H, 4.79; N, 4.47. Found: C, 65.30; H, 4.88; N, 4.65.

3,4-Dihydro-7-chloro-2,4-dimethyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**6e**).

This compound was obtained from **5e** (0.30 g, 1 mmole), 2*M* sodium hydroxide (1 ml) in 1,4-dioxane (5 ml) as white crystals, yield 0.18 g (64%), mp 151-153°; ir (potassium bromide): ν 3507 (NH), 2608 (COOH), 1704 (COOH), 1656 (CONH), 1480, 1399, 1358, 1268, 1115, 817, 640 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.61 (s, 3H, CH_3), 3.74 (s, 3H, N-CH_3), 7.29 (d, 1H, $J_{5,6}$ = 8.8 Hz, H_5), 7.38 (dd, 1H, $J_{5,6}$ = 8.8 Hz, $J_{6,8}$ = 2.4 Hz, H_6), 7.46 (d, 1H, $J_{6,8}$ = 2.4 Hz, H_8) ppm.

Anal. Calcd. for $C_{11}H_{10}ClNO_3S$: C, 48.61; H, 3.68; N, 5.16. Found: C, 48.19; H, 3.45; N, 4.82.

General Procedure B.

3,4-Dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**4a**).

To the solution of **3a** (0.50 g, 2 mmoles) in acetone (3 ml) and 0.1 *M* phosphate buffer (25 ml, *p*H 7), pig liver esterase (Sigma suspension, 2530U/ml, 0.05 ml = 15 drops) was added. The mixture was stirred for 15 hours at room temperature and neutralized with 0.1 *M* sodium hydroxide by using automatic titration system (dosimat system). When the reaction was completed, to the mixture 20 ml of chloroform was added. After the extraction with another 20 ml of chloroform, the denaturated enzymes were removed by filtration. The residue in water phase was acidified with 2 *M* hydrochloric acid to *p*H 2. The precipitated product was isolated by filtration and washed with ethanol to give 0.30 g (85%) of **4a**, with mp 164-165°; ir (potassium bromide): ν 3448 (NH), 1743 (COOH), 1665 (NH), 1588, 1484, 1381, 1238, 1119, 1010, 932, 858, 826, 747, 709, 681 cm^{-1}; optical rotation: +0.70° (c = 0.39 g/100 ml, methanol).

3,4-Dihydro-7-chloro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**4b**).

Compound **4b** was obtained from **3b** (0.58 g, 2 mmoles), acetone (3 ml) and 0.1 *M* phosphate buffer (25 ml, *p*H 7), pig liver esterase-PLE (Sigma suspension, 2530U/ml, 0.05 ml = 15 drops). After 6 days only 20 mg (4%) of **4b** were isolated. The optical rotation was minimal (0.5-1.0°).

Kinetic Resolution of Enantiomers.

General Procedure.

The Preparation of (+)-3,4-Dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**7a**) and (-)-3,4-Dihydro-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**7b**).

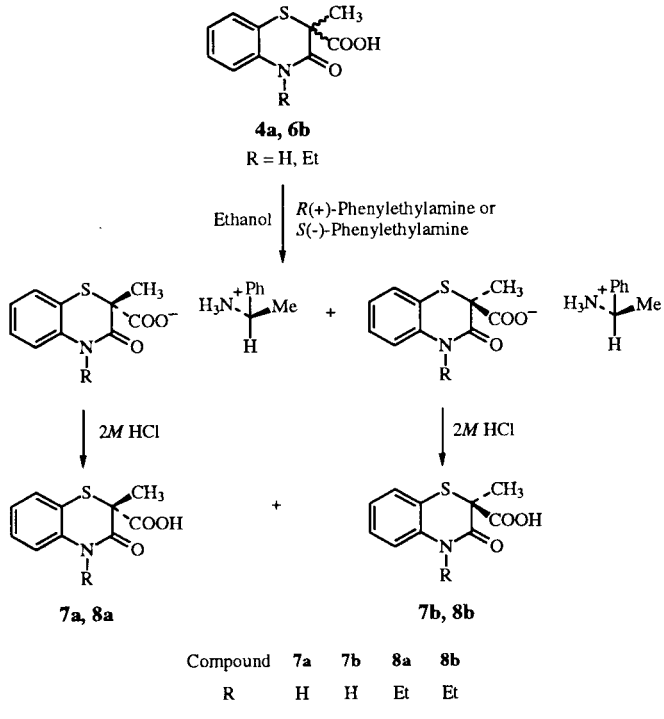
To the solution of **4a** (1.50 g, 6.7 mmoles) in 70 ml of ethanol, *S*(-)-phenylethylamine (0.81 g, 6.7 mmoles) was added. The precipitate (one diastereomeric salt) was filtered off, dissolved in water and acidified with 2*M* hydrochloric acid to *p*H 2. The product was filtered off and washed with cold ethanol to give 0.75 g of **7a** with optical rotation of +12.67° (0.39 g/100 ml, methanol), ir (potassium bromide): ν 3200 (NH), 2918 (COOH), 1706 (COOH), 1674 (CONH), 1586, 1482, 1374, 1280, 1127, 890, 751, 625 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.59 (s, 3H, CH_3), 6.97-7.32 (ABX_3 m, 4H, phenyl), 10.78 (s, 1H, NH) ppm.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.81; H, 4.04; N, 6.28. Found: C, 54.00; H, 3.80; N, 6.53.

The other diastereomeric salt was isolated by evaporating ethanol from the residue. After dissolving in water it was acidified with 2 *M* hydrochloric acid to *p*H 2 and filtered off. Then it was treated with *R*(+)-phenylethylamine. The procedure was the same as the procedure with *S*(-)-phenylethylamine. Compound **4a** (0.40 g, 1.79 mmoles), 20 ml of ethanol and *R*(+)-phenylethylamine (0.220 g, 1.79 mmoles) gave after the resolution 0.390 g of **7b** with optical rotation of-13.62° (0.40 g/100 ml, methanol); ir (potassium bromide): ν 3200 (NH), 2979 (COOH), 1708 (COOH), 1674 (CONH), 1586, 1482, 1280, 1126, 890, 751 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.58 (s, 3H, CH_3), 6.97-7.50 (ABX_3 m, 4H, phenyl), 10.77 (s, 1H, NH) ppm.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.81; H, 4.04; N, 6.28. Found: C, 54.40; H, 4.10; N, 6.62.

Scheme 2



(-)-3,4-Dihydro-4-ethyl-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**8a**) and (+)-3,4-Dihydro-4-ethyl-2-methyl-3-oxo-2*H*-benzo-1,4-thiazine-2-carboxylic Acid (**8b**).

These two compounds were obtained from **6b** (0.50 g, 2 mmoles), 30 ml of ethanol and *S*(-)-phenylethylamine (0.242 g, 2 mmoles). Product **8a** (0.06 g) had optical rotation -15,14° (0.40 g/100 ml, methanol), ir (potassium bromide): ν 3490 (NH), 2984 (COOH), 1734 (COOH), 1654 (CONH), 1576, 1448, 1403, 1116, 755 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.16 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.60 (s, 3H, CH_3), 3.80-4.00 (m, 1H, CH_2CH_3), 4.00-4.20 (m, 1H, CH_2CH_3), 7.00-7.50 (m, 4H, phenyl) ppm.

Anal. Calcd. for $C_{12}H_{13}NO_3S{\cdot}1/2H_2O$: C, 55.38; H, 5.38; N, 5.38. Found: C, 54.92; H, 5.06; N, 5.43.

The second resolution from **6b** (0.32 g, 1.27 mmoles), 10 ml ethanol and *R*(+)-phenylethylamine (0.154 g, 1.27 mmoles) gave after the resolution 0.10 g of **8b** with optical rotation of +11.91° (0.41 g/100 ml, methanol), ir (potassium bromide): ν 2996 (NH, COOH), 1728 (COOH), 1635 (CONH), 1584, 1474, 1449, 1393, 1198, 753, 637 cm^{-1}; ^1H nmr (DMSO-d_6, 300 MHz): δ 1.17 (t,

3H, J = 7.0 Hz, CH_2CH_3), 1.60 (s, 3H, CH_3), 3.80-4.00 (m, 1H, CH_2CH_3), 4.00-4.20 (m, 1H, CH_2CH_3), 7.00-7.39 (m, 4H, phenyl) ppm.

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.37; H, 5.18; N, 5.57. Found: C, 57.08; H, 5.04; N, 5.70.

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REFERENCES AND NOTES

[1] T. Aotsuka, H. Hosono, T. Kurihara, Y. Nakamura, T. Matusi, and F. Kobayashi, *Chem. Pharm. Bull.*, **42**, 1264 (1994).

[2] A. Ota, Y. Kawashima, H. Ohishi, and T. Ishida, *Chem. Pharm. Bull.*, **41**, 1681 (1993).

[3] L. D. Corona, G. Signorelli, A. Pinzetta, and G. Coppi, *Eur. J. Med. Chem.*, **27**, 419 (1992).

[4] R. C. M. Butler, C. B. Chapleo, and P. L. Myers, *J. Heterocyclic Chem.*, **22**, 177 (1985).

[5] J. Kapcho and C. F. Turk, *J. Med. Chem.*, **16**, 776 (1973).

[6] G. Trapani, A. Latrofa, A. Reho, M. Franco, and G. Liso, *J. Heterocyclic Chem.*, **29**, 1155 (1992).

[7] J. W. Worley, K. W. Ratts, and A. S. Cammack, *J. Org. Chem.*, **40**, 1731 (1975).

[8] V. Balasubramaniyan, P. Balasubramaniyan, and A. S. Shaikh, *Teterahedron*, **42**, 2731 (1986).

[9] D. Kikelj, E. Suhadolc, U. Urleb, and U. Zbontar, *J. Heterocyclic Chem.*, **30**, 597 (1993).

[10] E. W. Dehmlow and S. S. Dehmlow, Phase Transfer Catalysis, VCH Weinheim, 1983, p 136.

[11] J. M. Mcintosh, *J. Chem. Educ.*, **55**, 235 (1978).

[12] G. L. Isele and A. Lütringhans, *Synthesis*, 266 (1971).

[13] W. E. Keller, Phase transfer Reactions, Georg Thieme Verlag, Stuttgart, 1986, Vol **1**, p 35 and Vol **2**, p 120.

[14] S. M. Roberts, Preparative Biotransformations, John Wiley and Sons, West Sussex, 1993, England, pp 1:1.1-1:16.7.

[15] C. Tamm, *Pure Appl. Chem.*, **64**, 1887 (1992).

[16] H. G. Davies, R. H. Green, D. R. Kelly, and S. M. Roberts, Biotransformations in Preparative Organic Chemistry, Academic Press, London, 1989, p 25.

[17] R. L. Mital and S. K. Jain, *J. Chem. Soc. (C)*, 2148 (1969).