# 3-Oxo-1,2-benzoisothiazoline-2-acetic Acid 1,1-Dioxide Derivatives. I. Reaction of Esters with Alkoxides



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Reaction of 3-oxo-1,2-benzoisothiazoline-2-acetic acid alkyl esters 1,1-dioxide (**1a-d**) with alkaline alkoxides was carried out under various conditions. Under mild conditions, *o*-(*N*-carboxymethylsulfamyl)benzoic acids dialkyl esters (**2a-d**) were obtained with good yields. Reaction of **1a-d** or **2a-d** with sodium alkoxides under drastic conditions afforded 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid alkyl esters 1,1-dioxide (**3a-d**). Transesterification was observed when esters **1b-d** were treated with sodium methoxide in methanol. Esters **3a-d** were hydrolyzed in concentrated aqueous sodium hydroxide affording the acid **6**. Attempts to recrystallize **6** from water resulted in its decarboxylation to give 2*H*-1,2-benzothiazine-4-(3*H*)one 1,1-dioxide (**7**). Compound **6** could not be obtained by acid hydrolysis of esters **3a-d** or by rearrangement of 3-oxo-1,2-benzoisothiazoline-2-acetic acid 1,1-dioxide (**8**). Different experimental evidence supports the suggestion that rearrangement took place by ethanolysis of the carboxamide linkage affording the open sulfonamides (fast step) followed by a Dieckmann cyclization (slow step). It was demonstrated that transesterification took place in the open sulfonamides **2**.

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In 1956, Abe and co-workers (1) applied the base-induced rearrangement of phthalimides (Gabriel Colman reaction) (2) to *N*-phenacylsaccharin which gave the isomeric 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide. Later, Zinnes, *et al.* (3), applied this reaction to *N*-acetonylsaccharin, Lombardino (4) to saccharin-2-acetic acid methyl ester and Rasmussen (5) to the corresponding ethyl ester. In all cases ring expansion gave 1,2-benzothiazine 1,1-dioxides. In contrast, *N*-(α-phenylcarbethoxymethyl)saccharin gave a 1,3-benzothiazine (6).

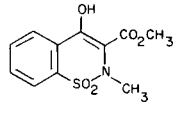
We report here our findings on the alkoxide-promoted reactions of several 3-oxo-1,2-benzoisothiazoline-2-acetic acid alkyl and aryl esters 1,1-dioxide (**1a-e**) (saccharin-2-acetic acid esters) under different conditions. Under mild conditions (stated in Table I), compounds **1a-d** reacted with 1-2 equivalents of sodium alkoxide in the corresponding absolute alcohol affording diesters of *o*-(*N*-carboxymethylsulfamyl)benzoic acid (**2a-d**) (7) (Scheme I).

The structure assignments of compounds **2a-d** were based on microanalysis and spectroscopic properties. Nmr spectra in deuteriochloroform show a triplet at $\delta \cong 6.90$ and a doublet at $\delta \cong 4.0$ for the NH and $CH_2$ groups, respectively. Upon deuteration the NH proton exchanged and the doublet collapsed into a singlet indicating coupling between the two groups and thus firmly establishing the $CH_2$-NH moiety.

By treatment of compounds **1a-d** with 2-4 equivalents sodium alkoxide in drastic conditions (stated in Table II), 1,2-benzothiazines **3a-d** were rapidly obtained (Scheme I) (8). Reaction of **1e** with sodium phenoxide resulted in a mixture of unresolved products.

Compounds **3a-d** were also obtained by cyclization of the open sulfonamides **2a-d**, respectively. The appearance in the nmr spectra of compounds **3a-d** of a singlet at $\delta \cong 11.5$ which disappears upon deuteration, and the positive ferric chloride test support the enolic form of these benzothiazines.

Reactions of **1a** with sodium methoxide in methanol under mild conditions were studied at different times and temperatures. Reaction at room temperature, for 1-20 minutes, afforded **2a** in very good yields. After 30 minutes, lower yields of **2a** and considerable amounts of water-soluble products were obtained. By carrying out the reaction for 6 hours, the benzothiazine **3a** was observed. Longer reaction times resulted in the disappearance of **3a** which was slowly transformed into the *N*-methyl derivative **4**. This reaction was complete in about 36 hours (8%), and




**4**

was accelerated by heating. Though we have made no extensive study on the transformation of **2a** to water-soluble products, is consistent with earlier reports of cleavage of sulfonamides by attack of basic reagents (9-15). Proctor (12) and others obtained sodium sulfinates by reaction of *N*-tosyl derivatives with alkoxides (12,13,15). Klamann, *et al.* (9,10), reported attainment of alkyl sulfonates from sulfonamides and sodium alkoxides. With excess of alkoxides, sodium sulfonates were obtained. Cleavage of the open sulfonamides **2a-d** would be favored by the presence

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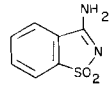
of electron acceptors groups (10). Experimental evidence leads to the conclusions that cleavage probably takes place affording mainly alkyl sulfonates. The formation of **4** from **3a** supports this suggestion. An attempt to identify a sodium sulfonate was performed by reaction with phosphorus pentachloride and ammonia. In these conditions only one product, the pseudo-saccharinamide (**5**) was isolated.



**5**

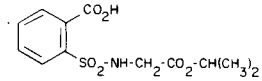
The optimum conditions for the preparation of benzothiazines **3a-d** (Table II) seem to be higher temperature and concentration of alkoxides than those required for the preparation of the open sulfonamides **2a-d**. Under these conditions the reaction was almost instantaneous for compounds **3a-c**; compound **3d** required a long reaction time (15 minutes).

If rearrangement of esters **1a-e** was carried out with alkoxides from different primary alcohols than that of the ester, transesterification took place. The same results were obtained by treatment of the open sulfonamides **2a-d** (Scheme II). Compound **1a** with sodium isopropoxide afforded a mixture of **3a** and **3c** in almost the same yield. With sodium tert-butoxide, no transesterification occurred (Table III). The greater steric hindrance of the *t*-butoxide compared with that of methoxide anion is presumably the reason for the slower rate of nucleophilic substitution.

Esters **3a-d** were stable in sodium alkoxide solutions, but were hydrolyzed in concentrated aqueous sodium hydroxide affording 2*H*-1,2-benzothiazin-4-(3*H*)one-3-carboxylic acid 1,1-dioxide (**6**) (Scheme III). The relative reactivity to the hydrolysis of the esters **3a-d** was determined by treating with 40% sodium hydroxide and is in agreement with the reactivity of esters of primary, secondary and tertiary alcohols (16). Reaction **3a** → **6** was complete in about 30 hours. In the same conditions **3c** requires 60 hours and **3d** was recovered almost unchanged after 5 days. Attempts to recrystallize **6** from water resulted in its decarboxylation and 2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide (**7**) was obtained. Compound **7** was also obtained by heating **3a-b** with concentrated hydrochloric acid.

Compound **6** could not be obtained by rearrangement of 3-oxo-1,2-benzoisothiazoline-2-acetic acid 1,1-dioxide (**8**). With 3 equivalents of sodium methoxide in mild conditions (3 minutes, room temperature), **8** afforded *o*-(*N*-carboxymethylsulfamyl)benzoic acid methyl ester (**9**). In more drastic conditions with 5 equivalents of sodium methoxide, **9** gave mainly water-soluble compounds. None of benzothiazines **6** or **7** were detected. The same results were obtained in attempts to cyclize **9** (Scheme III).

From a mechanistic point of view, the attainment of the open sulfonamides **2a-d** under mild conditions and their easy ring closure affording benzothiazines support the suggestion that rearrangement takes place by ethanolysis of the carboxamide linkage followed by a Dieckmann cyclization (3) (Scheme IV) (17). The fact that compound **6** could not be obtained by cyclization of **9** or ring expansion of **8** (Scheme III) may be explained since the α-carbon of acids fail to form the carbanion necessary in the Dieckmann cyclization. *o*-(*N*-Carboisopropoxymethylsulfamyl)benzoic acid (**10**) (7) failed to undergo ring closure because carboxylic acids do not have the necessary electrophilic character for such condensations.

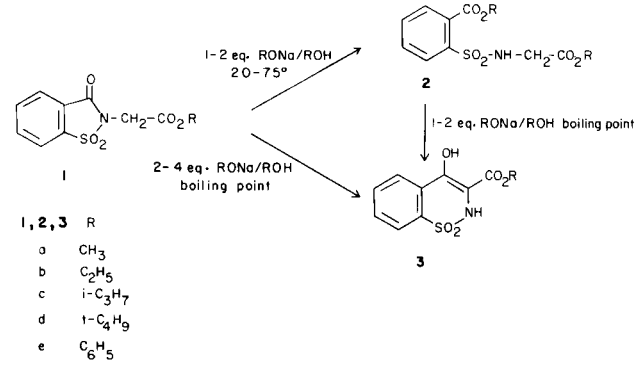


**10**

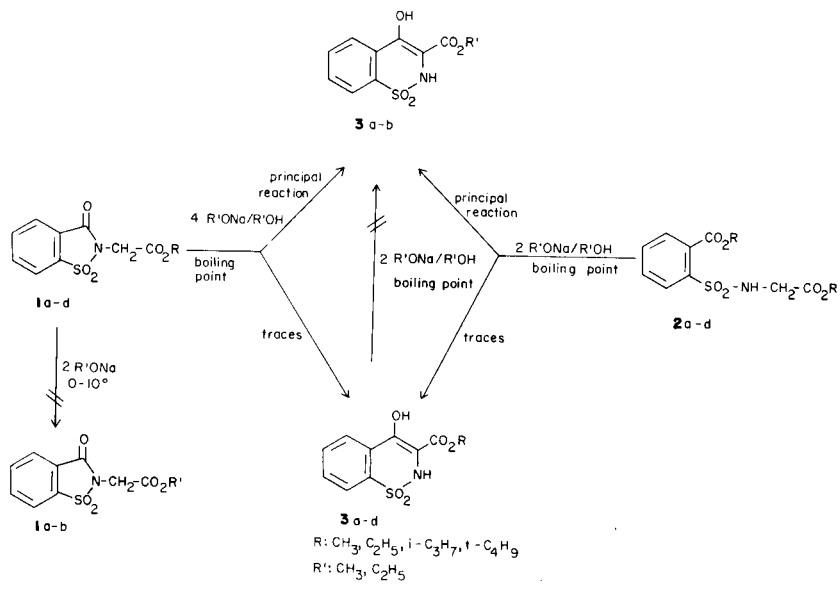
When reaction of **1d** with sodium *t*-butoxide was carried out under drastic conditions, the appearance of the open product **2d** is almost instantaneous, but ring expansion requires 15 minutes. This reaction period is substantially greater than that required for compound **1a-c** (3 minutes). This suggests that ring opening is the fast step and ring closure is the rate determining step.

The formation of open species are essential to explain transesterification. Compound **3b** was found to be stable to treatment with sodium methoxide under drastic conditions (Scheme II). On the other hand attempts to prepare compound **1a** from **1b** and sodium methoxide under very mild conditions (0-10°) were unsuccessful because the cleavage of the amide occurs almost instantaneously. These results suggest that transesterification occurs in the open sulfonamide. Direct evidence supporting these assumptions comes from the fact that compound **2a** could be prepared from **1b, 1c, 1e** and **2b** by mild treatment with 2 equivalents of sodium methoxide. When compound **1d** was treated with 2 equivalents of sodium methoxide (1.6*M* solution) at 75°, the rate of transesterification was

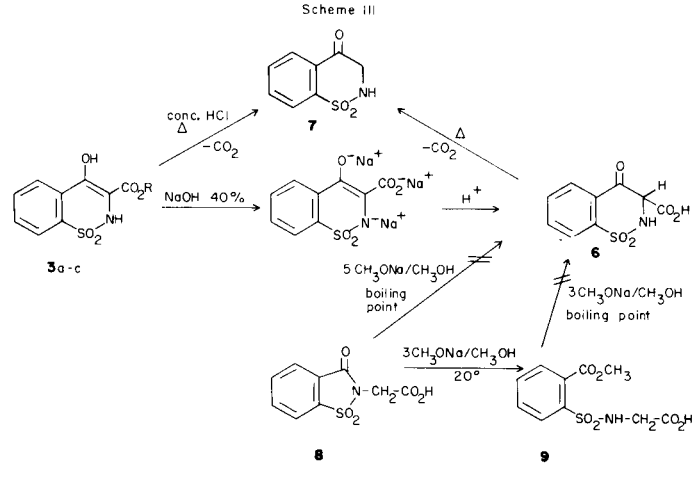
Scheme I



Scheme II




Scheme III




Scheme IV

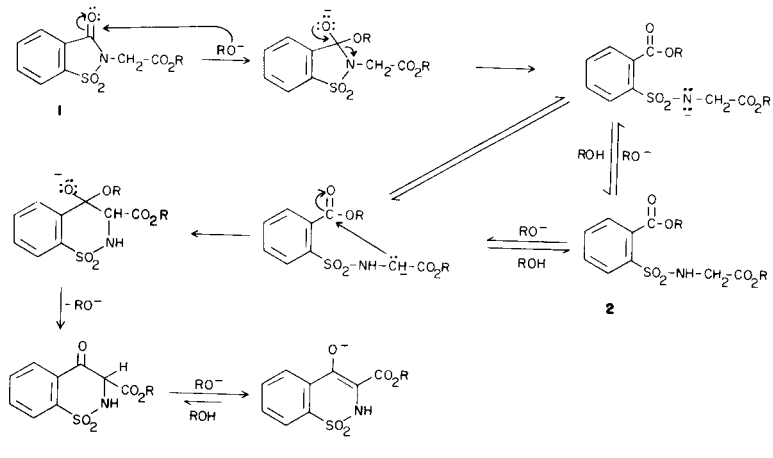
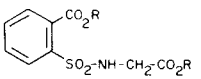


Table I

*o*-(*N*-Carboxymethylsulfamyl)benzoic Acid Dialkyl Esters (**2a-d**)

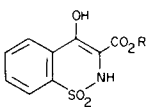



| Compound No. | Starting Materials | [RONa] | Conditions Temperature (°C) | Time (minutes) | Yield (a) % | M.p. (°C) | Recrystallization Solvent | | Analysis %C | %H | %N | %S | Ir $\nu$, $cm^{-1}$ | Spectroscopic Data Nmr (in deuteriochloroform) $\delta$, ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | **1a** + $CH_3ONa$ | 1.6*M* | 20 (b) | 1 | 92 | 98 | methanol | Calcd. | 45.99 | 4.53 | 4.88 | 11.15 | 3345 (NH) | 7.82-8.45 | (m) | (aromatic) |
| | | | | | | | | Found | 45.80 | 4.52 | 4.80 | 11.02 | 1765 (CO) | 6.95 | (t) (c) | (NH) |
| | | | | | | | | | | | | | 1735 (CO) | 4.26 | (s) | ($CH_3$) |
| | | | | | | | | | | | | | 1360 ($SO_2$) | 4.13 | (d) (d) | ($CH_2$) |
| | | | | | | | | | | | | | 1180 ($SO_2$) | 3.82 | (s) | ($CH_3$) |
| **2b** | **1b** + $C_2H_5ONa$ | 1.6*M* | 20 | 1 (e) | 88 | oil | f | Calcd. | 49.52 | 5.40 | 4.44 | 10.16 | 3300 (NH) (g) | 7.60-8.20 | (m) | (aromatic) |
| | | | | | | | | Found | 49.30 | 5.65 | 4.28 | 10.30 | 1750 (CO) | 6.85 | (t) (c) | (NH) |
| | | | | | | | | | | | | | 1720 (CO) | 4.58 | (q) | ($CH_2$) |
| | | | | | | | | | | | | | 1370 ($SO_2$) | 4.16 | (q) | ($CH_2$) |
| | | | | | | | | | | | | | 1160 ($SO_2$) | 4.03 | (d) (d) | ($CH_2$) |
| | | | | | | | | | | | | | | 1.58 | (t) | ($CH_3$) |
| | | | | | | | | | | | | | | 1.27 | (t) | ($CH_3$) |
| **2c** | **1c** + *i*-$C_3H_7ONa$ | 0.86*M* (h) | 60 (i) | 3 | 90 | 74 | ethanol | Calcd. | 52.48 | 6.12 | 4.08 | 9.33 | 3250 (NH) | 7.62-8.23 | (m) | (aromatic) |
| | | | | | | | | Found | 52.20 | 6.34 | 4.18 | 9.56 | 1750 (CO) | 6.80 | (t) (c) | (NH) |
| | | | | | | | | | | | | | 1725 (CO) | 5.47 | (m) | (CH) |
| | | | | | | | | | | | | | 1360 ($SO_2$) | 5.04 | (m) | (CH) |
| | | | | | | | | | | | | | 1180 ($SO_2$) | 4.00 | (d) (d) | ($CH_2$) |
| | | | | | | | | | | | | | | 1.55 | (d) | ($CH_3$) |
| | | | | | | | | | | | | | | 1.27 | (d) | ($CH_3$) |
| **2d** | **1d** + *t*-$C_4H_9ONa$ | 1.5*M* | 75 (i) | 3 | 86 | 120 | ethanol | Calcd. | 54.99 | 6.74 | 3.77 | 8.62 | 3280 (NH) | 7.62-8.25 | (m) | (aromatic) |
| | | | | | | | | Found | 54.70 | 6.96 | 3.70 | 8.54 | 1750 (CO) | 6.70 | (t) (c) | (NH) |
| | | | | | | | | | | | | | 1720 (CO) | 3.95 | (d) (d) | ($CH_2$) |
| | | | | | | | | | | | | | 1340 ($SO_2$) | 1.80 | (s) | ($CH_3$) |
| | | | | | | | | | | | | | 1180 ($SO_2$) | 1.46 | (s) | ($CH_3$) |

(a) Given yields were obtained with 2 equivalents of sodium alkoxide. With 1-1.5 equivalents, lower yields were observed. (b) Reaction could be performed at higher temperatures (50-70°) without appearance of **3a**. (c) Exchangeable. (d) Upon deuteration the doublet collapsed into a singlet. (e) By prolonged reaction **3b** was observed. (f) The oil was purified by plc (9:1 benzene-methanol). (g) Ir was carried out in film. (h) With sodium isopropoxide solutions of higher concentration considerable amounts of **3c** were obtained. (i) Due to the low solubility of the sodium alkoxide in alcohol, reaction could not be performed at room temperature.

Table II

4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxylic Acid Alkyl Ester 1,1-Dioxides (**3a-d**)




| Compound No. | Starting Materials | Conditions (a) [RONa] | Time (minutes) | Yield (b) % | M.p. (°C) | Recristallization Solvent | Previous Reference | | Analysis %C | %H | %N | %S | Spectroscopic Data Ir $\nu$, $cm^{-1}$ | Nmr (in deuteriochloroform) $\delta$, ppm |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | **1a** + $CH_3ONa$ | 3.2*M* | 3 | 70 | 171 | methanol | 4 | | | | | | 3240 (NH)<br>1660 (CO)<br>1350 ($SO_2$)<br>1170 ($SO_2$) | 11.5 (s) (c) (OH)<br>7.75-8.35 (m) (aromatic)<br>6.50 (s) (c) (NH)<br>4.10 (s) ($CH_3$) |
| **3b** | **1b** + $C_2H_5ONa$ | 3.2*M* | 3 | 62 | 140 | acetone | 5 | | | | | | 3280 (NH)<br>1680 (CO)<br>1350 ($SO_2$)<br>1180 ($SO_2$) | 11.5 (s) (c) (OH)<br>7.80-8.40 (m) (aromatic)<br>6.66 (s) (c) (NH)<br>4.65 (q) ($CH_2$)<br>1.62 (t) ($CH_3$) |
| **3c** | **1c** + *i*-$C_3H_7ONa$ | 2.5*M* | 5 | 85 | 170 | ethanol | | Calcd.<br>Found | 50.88<br>50.65 | 4.59<br>4.82 | 4.95<br>4.78 | 11.31<br>11.20 | 3200 (NH)<br>1660 (CO)<br>1340 ($SO_2$)<br>1190 ($SO_2$) | 11.5 (s) (c) (OH)<br>7.70-8.32 (m) (aromatic)<br>6.65 (s) (c) (NH)<br>5.42 (m) (CH)<br>1.55 (d) ($CH_3$) |
| **3d** | **1d** + *t*-$C_4H_9ONa$ | 2.3*M* | 15 (d) | 64 | 157 | ethanol | | Calcd.<br>Found | 52.52<br>52.30 | 5.05<br>5.30 | 4.71<br>4.68 | 10.77<br>10.90 | 3250 (NH)<br>1660 (CO)<br>1340 ($SO_2$)<br>1180 ($SO_2$) | 11.5 (s) (c) (OH)<br>7.56-8.15 (m) (aromatic)<br>6.66 (s) (c) (NH)<br>1.6 (s) ($CH_3$) |

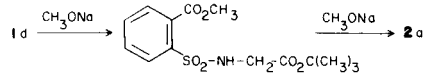
(a) All reactions were carried out at the boiling point of the mixture reaction. (b) Given yields were obtained with 4 equivalents of sodium alkoxides. With 2-3 equivalents, lower yields were observed. (c) Exchangeable. (d) With lower times of reaction considerable amounts of **2d** were obtained.

Table III

| Starting Material | Alkoxide | Reaction Products (a) | Yield (%) |
|---|---|---|---|
| **1a** | $C_2H_5ONa$ | **3b** | 74 |
| | | **3a** | 2 |
| **1a** | $i$-$C_3H_7ONa$ | **3a** | 32 |
| | | **3c** | 36 |
| **1a** | $t$-$C_4H_9ONa$ | **3a** | 72 |
| | | **3d** | 3 |
| **1b** | $CH_3ONa$ | **3a** | 76 |
| **1c** | $CH_3ONa$ | **3a** | 78 |
| **1d** | $CH_3ONa$ | **3a** | 75 |
| **1e** | $CH_3ONa$ | **3a** | 82 |

(a)The products were isolated by plc.

Scheme V

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substantially slower than ring opening and after 5 minutes, *o*-(*N*-carbo-*t*-butoximethylsulfamyl)benzoic acid methyl ester (**11**) was isolated. In 12 minutes transesterification was completed and compound **2a** was the only product of the reaction (Scheme V).

## EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. Ir spectra were recorded on a Beckman 20 A instrument using potassium bromide pellets unless stated otherwise. Nmr spectra were obtained on a Perkin Elmer R 12 (60 MHz) spectrometer with tetramethylsilane as internal reference. Chemical shifts are reported in parts per million ($\delta$) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). The presence of exchangeable protons was confirmed by use of deuterium oxide. Analytical tlc was carried out on 10 × 20 cm glass plates coated with Merck Silica Gel HF254 + 366. Preparative thin layer separations (plc) were performed on Silica Gel HF254 on 40 × 20 × 0.15 cm layers. Reagents, solvents, and starting materials were purchased from standard sources and purified according to literature procedures.

3-Oxo-1,2-benzoisothiazoline-2-acetic Acid Ester 1,1-Dioxides (**1a-e**). General Procedure.

A mixture of 0.12 mole of benzoisothiazoline-3-one 1,1-dioxide sodium salt, 0.08 mole of chloroacetic acid alkyl or aryl ester and 15 ml. of *N*,*N*-dimethylformamide was heated at 120° for 6 hours. The reaction mixture was poured into ice water and the resulting solid was filtered, washed with water and dried. The crude product was recrystallized from ethanol.

Compounds **1a** and **1b** were described by Eckenroth and Koerppen (20).

Compound **1c** (75% yield) had m.p. 117°; ir: 2980 (C-H), 1750 (C=O), 1730 (C=O), 1320 ($SO_2$) and 1180 $cm^{-1}$ ($SO_2$); nmr (deuteriochloroform): $\delta$ 8.38-7.90 (m, 4, aromatic), 5.31 (m, 1, C-H), 4.60 (s, 2, $CH_2$) and 1.47 (d, 6, $CH_3$).

*Anal.* Calcd. for $C_{12}H_{13}NO_5S$: C, 50.82; H, 4.59; N, 4.95; S, 11.30. Found: C, 50.80; H, 4.74; N, 4.80; S, 11.50.

Compound **1d** (60% yield) had m.p. 133°; ir: 2980 (C-H), 1760-1730 (C=O), 1330 ($SO_2$) and 1180 $cm^{-1}$ ($SO_2$); nmr (deuteriochloroform): $\delta$ 8.43-7.90 (m, 4, aromatic), 4.54 (s, 2, $CH_2$) and 1.65 (s, 9, $CH_3$).

*Anal.* Calcd. for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.05; N, 4.71; S, 10.77. Found: C, 52.60; H, 5.20; N, 4.85; S, 10.95.

Compound **1e** (68% yield) had m.p. 113°; ir: 1795 (C=O), 1750 (C=O), 1350 ($SO_2$) and 1180 $cm^{-1}$; nmr (deuteriochloroform): $\delta$ 8.42-7.95 (m, 4, $C_6H_4$), 7.75-7.28 (m, 5, $C_6H_5$) and 4.95 (s, 2, $CH_2$).

*Anal.* Calcd. for $C_{15}H_{11}NO_5S$: C, 56.78; H, 3.47; N, 4.42; S, 10.09. Found: C, 56.95; H, 3.60; N, 4.32; S, 10.00.

2-(*N*-Carboxymethylsulfamyl)benzoic Acid Dialkyl Esters (**2a-d**). General Procedure.

A solution of sodium alkoxide was prepared from 0.46 g. of sodium (0.02 mole) in the corresponding absolute alcohol. The solution was heated at the appropriate temperature and 0.01 mole of 3-oxo-1,2-benzoisothiazoline-2-acetic acid alkyl ester 1,1-dioxide (**1a-d**) was added all at once as the powder. After a few minutes the reaction was quenched by pouring into concentrated hydrochloric acid-ice. If the product crystallized (some times scratching with a glass rod was necessary), it was collected, washed with water and recrystallized. If not, the emulsion was extracted three times with chloroform. After washing with water, the organic solution was dried, concentrated *in vacuo* and the resulting product was purified by recrystallization or plc. Details of the reaction (temperature, time, alkoxide concentration, yields, melting points, recrystallization solvents), elemental analysis and spectroscopic data of the compounds are given in Table I.

Influence of Temperature and Time of Reaction of **1a** with Sodium Methoxide in Mild Conditions.

Sampling was carried out at suitable time intervals, acidified, filtered off, and the solid analyzed by tlc (9:1 benzene-methanol). In conditions stated in Table I, **2a** was obtained in good yields. After 30 minutes it was partially transformed in water-soluble compounds. Six hours afterwards, **3a** was detected. Four hours later, a new spot appeared, which after 36 hours of reaction was the sole product isolated. It was identified as 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (**4**) by comparison with an authentical sample (4), m.p. and mixed m.p. 163-165° (8% yield).

By carrying out the reaction at 75°, **3a** was detected after 15 minutes, and after 1 hour, only **4** was obtained.

In attempts to identify the water-soluble compounds, a portion of the reaction mixture was acidified with concentrated hydrochloric acid, filtered to remove compound **4** and concentrated *in vacuo* at room temperature. The residue was extracted with absolute alcohol affording a very hygroscopic mixture of mainly four products. 1 g. of this mixture was treated with 2 g. of phosphorus pentachloride and heating in steam bath until the reaction started. When the reaction stopped, 15 ml. of water was carefully added. The aqueous layer was separated and the residue was washed with ice-water. After adding 5 ml. of concentrated ammonia, the solution was heated for a few minutes and cooled affording 85 mg. of a white solid, m.p. 308° (water). Elemental analysis and spectroscopic properties suggest for this compound the structure of 3-amino-1,2-benzoisothiazole 1,1-dioxide (pseudo-saccharinamide) (5) (21); ir: 3330 (NH), 1670 (C=N), 1300 ($SO_2$) and 1160 $cm^{-1}$ ($SO_2$); nmr (DMSO-$d_6$): $\delta$ 9.07 (s, 2, exchangeable, $NH_2$) and 8.36-7.73 (m, 4, aromatic).

*Anal.* Calcd. for $C_7H_6N_2O_2S$: C, 46.15; H, 3.30; N, 15.38; S, 17.58. Found: C, 46.15; H, 3.55; N, 15.55; S, 17.75.

4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxylic Acid Alkyl Esters 1,1-Dioxide (**3a-d**).

A. From 3-Oxo-1,2-benzoisothiazoline-2-acetic Acid Alkyl Esters 1,1-Dioxide (**1a-d**).

A solution of sodium alkoxide was prepared from 0.92 g. of sodium (0.04 mole) in the corresponding absolute alcohol. The solution was refluxed in an oil bath and 0.01 mole of 3-oxo-1,2-benzoisothiazoline-2-acetic acid alkyl ester 1,1-dioxide (**1a-d**) was added all at once as the powder. After a few minutes, the orange slurry was poured into ice-

concentrated hydrochloric acid. The solid was filtered off, washed with water and recrystallized affording compounds **3a-d** (8). Details of reaction (time, alkoxide concentration, melting points, recrystallization solvents), elemental analysis and spectroscopic data of the compounds are given in Table II.

Attempts to rearrange **1e** with sodium phenoxide in methanol following the general procedure, resulted in the formation of an unpurifiable complex mixture.

B. From *o*-(*N*-Carboxymethylsulfamyl)benzoic Acid Dialkyl Esters (**2a-d**).

The reaction was carried out in the same manner as above but using 0.46 g. of sodium (0.02 mole) in the appropriate volume of alcohol.

Attempts to cyclize **10** (7) with sodium isopropoxide in 2-propanol were unsuccessful.

Compounds **3a-d** gave positive ferric chloride test and remained unchanged by heating with sodium alkoxide in alcohol ([RONa]: 0.8-1.64*M*) for 1 hour. By heating with more concentrated sodium alkoxides, some of the compounds were transformed in resinous products.

2*H*-1,2-Benzothiazin-4(3*H*)one-3-carboxylic Acid 1,1-Dioxide (**6**).

Compound **3a** (1.0 g.) in 5 ml. of aqueous 40% sodium hydroxide was allowed to stand at room temperature for 28 hours. The reaction mixture was then filtered and acidified in ice bath with cold concentrated hydrochloric acid as rapidly as was consistent with maintaining the temperature at 30-35°. The crude product was filtered off and purified by dissolution in cold 10% sodium hydroxide. The alkaline solution was extracted with chloroform and the resulting aqueous solution was acidified in ice bath with concentrated hydrochloric acid. The white precipitate was filtered off, washed with water and dried at room temperature to give **6** (70% yield) (22); ir: 3260 (NH), 2900 (OH), 1668 (C=O), 1330 ($SO_2$) and 1180 $cm^{-1}$ ($SO_2$); nmr (DMSO-$d_6$): $\delta$ 9.9 (broad s, 1, exchangeable, $CO_2H$), 8.55 (d, 1, exchangeable, NH), 8.00-7.60 (m, 4, aromatic), 6.25 (d, 1, upon deuteration collapsed into a singlet, CH).

*Anal.* Calcd. for $C_9H_7NO_5S$: C, 44.82; H, 2.90; N, 5.80; S, 13.28. Found: C, 44.65; H, 3.05; N, 5.61; S, 13.00.

Compound **6** shows a negative ferric chloride test. It could not be recrystallized from organic solvents. Attempts of recrystallization from water result in abundant evolution of carbon dioxide and 2*H*-1,2-benzothiazine-4-(3*H*)one-1,1-dioxide (**7**) was obtained. Structure of **7** was confirmed by comparison with an authentic sample (23), m.p. and mixed m.p. 157°; nmr (DMSO-$d_6$): $\delta$ 8.60 (t, 1, exchangeable, NH), 8.13-7.78 (m, 4, aromatic) and 4.33 (d, 2, upon deuteration collapsed into a singlet, $CH_2$).

Compound **7** was also obtained in essentially quantitative yields when 2 g. of **3a-b** were refluxed 9 hours with 10 ml. of concentrated hydrochloric acid.

The relative reactivity to saponification of esters **3** was studied by treating compounds **3a**, **3c** and **3d**, with aqueous 40% sodium hydroxide (0.7*M* solution). The reaction was monitored by tlc (9:1 benzene-methanol). In compound **3a** after 30 minutes, compound **6** was detected and the reaction was completed in 28 hours. In compound **3c** under the same conditions **6** was observed after 8.5 hours and the reaction was completed in 60 hours. Compound **3d** was recovered almost unchanged after 5 days.

Attempted Synthesis of 2*H*-1,2-Benzothiazine-4-(3*H*)one-3-carboxylic Acid 1,1-Dioxide (6) from 3-Oxo-1,2-benzoisothiazoline-2-acetic Acid 1,1-Dioxide (8).

A.

Treatment of **8** (24) with 5 equivalents of sodium methoxide in methanol following the same procedure as for the preparation of **3a** gave mainly water-soluble products and 30% of an oil which showed a mixture of unidentified products by tlc.

B.

Reaction of **8** with 3 equivalents of sodium methoxide under the same conditions as for compound **2a**, afforded *o*-(*N*-carboxymethylsulfamyl)-benzoic acid methyl ester (**9**) (79% yield); m.p. 145° (methanol); ir: 3250 (NH), 1740 (C=O), 1720 (C=O), 1300 ($SO_2$) and 1170 $cm^{-1}$ ($SO_2$); nmr (DMSO-$d_6$): $\delta$ 8.15-7.71 (m, 4, aromatic), 7.75 (s, 1, exchangeable, overlapped with the aromatic multiplet, $CO_2H$), ca. 7.67 (broad signal, 1, exchangeable, partially overlapped with the aromatic multiplet, NH), 3.92 (s, 3, $CH_3$) and 3.81 (d, 2, upon deuteration collapsed into a singlet, $CH_2$).

*Anal.* Calcd. for $C_{10}H_{11}NO_6S$: C, 43.96; H, 4.03; N, 5.13; S, 11.72. Found: C, 43.74; H, 4.28; N, 5.10; S, 11.89.

Attempts to cyclize **9** with 3 equivalents of sodium methoxide under drastic conditions were unsuccessful.

Transesterifications.

The results obtained from reaction in drastic conditions of esters **1a-e** with alkoxides from different alcohols than the ester are summarized in Table III. Similar results were obtained starting from the open sulfonamides **2a-d**.

Compounds **1b, 1c, 1e** and **2b** by treatment with sodium methoxide for 5 minutes in mild conditions afforded **2a**. In the same conditions **1d** afforded *o*-(*N*-carbo-*t*-butoxymethylsulfamyl)benzoic acid methyl ester (**11**) (85% yield), m.p. 86° (ethanol); ir: 3250 (NH), 1745 (C=O), 1730 (C=O), 1360 ($SO_2$) and 1180 $cm^{-1}$ $SO_2$; nmr (deuteriochloroform): $\delta$ 8.32-7.67 (m, 4, aromatic), 6.78 (t, 1, exchangeable, NH), 4.18 (s, 3, $CH_3$), 3.95 (d, 2, $CH_2$, upon deuteration collapsed into a singlet) and 1.47 (s, 9, $CH_3$).

*Anal.* Calcd. for $C_{14}H_{19}NO_6S$: C, 51.06; H, 5.77; N, 4.26; S, 9.73. Found: C, 51.30; H, 5.98; N, 4.05; S, 9.51.

When the reaction was carried out for 12 minutes, **1d** afforded **2a** as the sole product (68% yield).

When **3a** was treated with sodium ethoxide in drastic conditions, it remained almost unchanged and only traces of **3b** were detected.

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(7) With sodium isopropoxide in technical isopropanol containing 0.5% of water, **1c** afforded *o*-(*N*-carboisopropoximethylsulfamyl)benzoic acid (**10**), m.p. 112° (benzene). It was identified by elemental analysis and spectrscopic data.

(8) It is interesting to note that Lombardino, *et al.* (4) reported that reaction of **1a** with sodium methoxide in methanol fails to produce any detectable product. This observation was verified by Rasmussen (5). No experimental details were given by Lombardino, but probably, in agreement with our results they did not use the necessary drastic conditions for cyclization, and the open sulfonamide **2a** was transformed in water-soluble compounds.

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