## THE SYNTHESIS OF CYCLIC ANALOGUES OF TOLBUTAMIDE

# D. L. Simmons, J. M. Dodsworth, and Francis L. Chubb

Since the original synthesis of 3-oxo-3,4-dihydro-1,2,4-benzothiadiazine (1) relatively few derivatives of this compound have been reported (2, 3). More recently sulphamyl substituted 3-oxo-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides have been synthesized as potential diuretics (4, 5) and as intermediates in the synthesis of diuretics (6, 7). These compounds are cyclic sulphonylureas, since they contain the  $-SO_2NHCONH-$  group in the heterocyclic ring. In this communication we wish to report the synthesis of a series of substituted 3-oxo-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides (I) which may be considered as cyclic analogues of the hypoglycemic sulphonylureas such as tolbutamide (II).



These compounds were obtained from the corresponding 2-sulphamylanilines by treatment with phosgene (7). In the case of the 2-sulphamylanilines (III) with no substituent on the aniline nitrogen, treatment with phosgene yielded the final products directly. However, when the N-butyl-2-sulphamylanilines (IV) were treated with phosgene, the intermediate N-carbonyl chlorides (V) were isolated. Treatment with base effected ring closure to yield I. The N-butyl-2-sulphamylanilines were obtained by acylation of the corresponding anilines (4) with *n*-butyryl chloride followed by reduction with lithium aluminum hydride. The anilines were obtained from the appropriate 2-chloronitrobenzene according to the procedure of Topliss, Sperber, and Rubin (8). The pharmacology of these compounds will be reported elsewhere.

## EXPERIMENTAL

Melting points are uncorrected. Microanalyses were carried out at the microanalytical laboratory of C. Daesslé, 5757 Decelles Avenue, Montreal, Quebec. Infrared spectra were obtained on a Perkin-Elmer spectrophotometer Model 237. Ultraviolet spectra were obtained on a Beckman DK2 spectrophotometer.

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<sup>5-</sup>Methyl-2-sulphamylaniline

<sup>5-</sup>Methyl-2-sulphamylaniline was prepared in 15% overall yield from 2-chloro-5-methylnitrobenzene according to the procedure of Topliss, Sperber, and Rubin (8). It crystallized from benzene and melted at 125–126°.  $\lambda_{max}^{MooH}$  246 m $\mu$  (7800), 304 m $\mu$  (3630). Anal. Calculated for C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S: C, 45.14; H, 5.41; N, 15.04; S, 17.21. Found: C, 45.14; H, 5.38; N, 15.58; S, 17.60.



### 5-Chloro-2-sulphamylaniline

5-Chloro-2-sulphamylaniline was obtained from 2,5-dichloronitrobenzene by the above procedure in 22% yield, and melted at  $143-145^{\circ}$  (reported  $144-146^{\circ}$ ) (9).

## $\label{eq:solution} 3-Oxo-6-trifluoromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide$

3-Oxo-6-trifluoromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide was prepared by the action of phosgene on 5-trifluoro-2-sulphamylaniline (4) according to the procedure of Close, Swett, and Nordeen (7) and was isolated in 89% yield. It crystallized from ether – petroleum ether and melted at 227°.  $\lambda_{max}^{MeOH}$  244 m $\mu$  (10,800), 295 m $\mu$  (2,320);  $\nu_{max}^{Nujol}$  3550 cm<sup>-1</sup>, 3510 cm<sup>-1</sup>, 1748 cm<sup>-1</sup> (strong), 1648 cm<sup>-1</sup> (weak). Anal. Calculated for C<sub>8</sub>H<sub>5</sub>N<sub>2</sub>SO<sub>3</sub>F<sub>3</sub>: C, 36.09; H, 1.89; N, 10.53; S<sub>7</sub>-12.04. Found: C, 36.02; H, 1.98; N, 10.40; S, 12.60.

### 6-Methyl-3-oxo-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide

6-Methyl-3-oxo-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide was obtained in 89% yield by the action of phosgene on 5-methyl-2-sulphamylaniline. It crystallized from alcohol-water and melted at 298-300°.  $\lambda_{\max}^{MeOH}$  243 m $\mu$  (11,600), 287 m $\mu$  (1,740);  $\nu_{\max}^{Nulol}$  3208 cm<sup>-1</sup>, 1716 cm<sup>-1</sup>. Anal. Calculated for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>SO<sub>3</sub>: C, 45.27; H, 3.80; N, 13.20; S, 15.11. Found: C, 45.39; H, 3.83; N, 13.45; S, 15.03.

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6-Chloro-3-oxo-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide was prepared by the action of phosgene on 5-chloro-2-sulphamylaniline in 88% yield. It crystallized from alcohol and melted at 300° decomp.  $\lambda_{max}^{MeOH}$  245 m $\mu$  (10,000), 292.5 m $\mu$  (2,000);  $\nu_{max}^{Nijol}$  3290 cm<sup>-1</sup>, 1685 cm<sup>-1</sup>. Anal. Calculated for C<sub>7</sub>H<sub>5</sub>N<sub>2</sub>ClSO<sub>3</sub>: C, 36.14; H, 2.17; N, 12.04; S, 13.78. Found: C, 35.87; H, 2.26; N, 12.47; S, 13.95.

### N-Butyryl-2-sulphamyl-5-trifluoromethylaniline

N-Butyryl-2-sulphamyl-5-trifluoromethylaniline was prepared from 2-sulphamyl-5-trifluoromethylaniline (4) by treatment with *n*-butyryl chloride in dioxane according to the procedure of Novello *et al.* (4). It separated from benzene as needles and melted at 135–136°.  $\lambda_{max}^{MooH}$  247 m $\mu$  (13,500), 292 m $\mu$  (3,800). Anal. Calculated for C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>SF<sub>3</sub>: C, 42.59; H, 4.19; N, 9.03. Found: C, 42.79; H, 3.98; N, 9.33.

#### N-Butyryl-5-methyl-2-sulphamylaniline

N-Butyryl-5-methyl-2-sulphamylaniline was prepared in 90% yield by the action of *n*-butyryl chloride on 5-methyl-2-sulphamylaniline as described above. It crystallized from alcohol as prisms and melted at 135–137°.  $\lambda_{\max}^{MoH}$  247.5 m $\mu$  (12,900), shoulder 283 m $\mu$  (2,560), shoulder 288 m $\mu$  (2,480). Anal. Calculated for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S: C, 51.54; H, 6.29; N, 10.93; S, 12.51. Found: C, 51.65; H, 6.67; N, 11.08; S, 12.24.

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### N-Butyryl-5-chloro-2-sulphamylaniline

N-Butyryl-5-chloro-2-sulphamylaniline was prepared in 87% yield by the action of n-butyryl chloride on 5-chloro-2-sulphamylaniline as described above. It crystallized from benzene as prisms and melted at 141–142°.  $\lambda_{\max}^{MeOH}$  248.5 m $\mu$  (15,200), shoulder 286.5 m $\mu$  (2,500), shoulder 292 m $\mu$  (2,450). Anal. Calculated for C10H13N2O3SCI: C, 43.40; H, 4.73; N, 10.13; Cl, 12.81. Found: C, 43.63; H, 4.79; N, 10.27; Cl, 12.84.

#### N-Butyl-2-sulphamyl-5-trifluoromethylaniline

N-Butyryl-2-sulphamyl-5-trifluoromethylaniline (2.23 g) was added portionwise and with stirring to a suspension of lithium aluminum hydride (0.7 g) in hydride-stable tetrahydrofuran (50 cc). After the addition was complete, the contents were gently refluxed for 3 hours. The excess hydride was destroyed by careful addition of ethyl acetate and water, and the contents then concentrated in vacuo. Water (100 ml) was added and the solution made acidic with concentrated phosphoric acid and extracted with ether. Evaporation of the dried ethereal extracts *in vacuo* provided a white solid (2.0 g) which crystallized from ether – petroleum ether as fine needles, m.p. 140–141°.  $\lambda_{\text{max}}^{\text{MeOH}}$  254 m $\mu$  (20,000), 330 m $\mu$  (10,000). Anal. Calculated for C<sub>11</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub>SF<sub>8</sub>: C, 44.59; H, 5.07; N, 9.46. Found: C, 44.80; H, 5.51; N, 9.69.

#### N-Butyl-5-methyl-2-sulphamylaniline

N-Butyl-5-methyl-2-sulphamylaniline was prepared in 75% yield from the N-butyryl derivative according to the procedure described above. It crystallized from ether – petroleum ether as needles and melted at 112°.  $\lambda_{max}^{MoOH}$  253 m $\mu$  (18,000), 315 m $\mu$  (9,700). Anal. Calculated for C<sub>11</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S: C, 54.52; H, 7.49; N, 11.56; S, 13.23. Found: C, 54.66; H, 7.51; N, 11.75; S, 13.29.

#### N-Butyl-5-chloro-2-sulphamylaniline

N-Butyl-5-chloro-2-sulphamylaniline was obtained in 79% yield from the N-butyryl derivative by the above procedure. It crystallized from ether – petroleum ether as needles and melted at 119°.  $\lambda_{max}^{MeOH}$  255.5 m $\mu$ (19,460), 320 mµ (10,000). Anal. Calculated for C10H15N2SO2Cl: C, 45.71; H, 5.75; N, 10.66; S, 12.20. Found: C, 45.98; H, 5.94; N, 10.77; S, 12.22.

## N-Butyl-N-chlorocarbonyl-5-methyl-2-sulphamylaniline

N-Butyl-N-chlorocarbonyl-5-methyl-2-sulphamylaniline was prepared by the same procedure used in the preparation of the 3-oxo-benzothiadiazines (7) and was isolated in 92% yield. It crystallized from ether petroleum ether and melted at 98°.  $\nu_{m,x}^{CHCl_3}$  3500 cm<sup>-1</sup>, 3450 cm<sup>-1</sup>, 3275 cm<sup>-1</sup>, 1745 cm<sup>-1</sup>, 1718 cm<sup>-1</sup>. Anal. Calculated for C<sub>12</sub>H<sub>17</sub>N<sub>2</sub>SO<sub>3</sub>Cl: C, 47.28; H, 5.62; N, 9.19; S, 10.52; Cl, 11.63. Found: C, 47.05; H, 5.48; N, 9.36; S, 10.68; Cl, 11.58.

The corresponding 5-chloro- and 5-trifluoro-methyl analogues failed to crystallize and were employed in the following reactions without further purification. Infrared spectroscopy of these products revealed the characteristic doublet of carbonyl chlorides in the  $1715-1750 \text{ cm}^{-1}$  region.

### 4-Butyl-6-methyl-3-oxo-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide

The N-carbonyl chloride derivative (0.69 g) was gently refluxed with 5% methanolic potassium hydroxide (20 ml) for 1 hour. The reaction mixture was then cooled, diluted with water, and extracted with ether. The aqueous extract was acidified with concentrated hydrochloric acid and extracted with ether. Evaporation of the dried ethereal extracts (acidic) provided a white solid (0.65 g) which crystallized from methylene chloride – petroleum ether and melted at 173–174°.  $\lambda_{max}^{MeOH}$  250 m $\mu$  (11,100), 290 m $\mu$  (1,960);  $\nu_{max}^{CHCl_2}$  3350 cm<sup>-1</sup>, 1700 cm<sup>-1</sup>. Anal. Calculated for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S: C, 53.71; H, 6.01; N, 10.44; S, 11.95. Found: C, 53.96; H, 5.78; N, 10.75; S, 11.99.

## $\label{eq:alpha} 4-Butyl-3-oxo-6-trifluoromethyl-3, 4-dihydro-1, 2, 4-benzothiadiazine-1, 1-dioxide$

N-Butyl-3-oxo-6-trifluoromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide was prepared in 90% yield from the oily N-carbonyl chloride derivative by the above procedure. It crystallized from ether – petro-leum ether and melted at 144°.  $\lambda_{max}^{MeOH}$  250.5 m $\mu$  (12,690), 298 m $\mu$  (2,660);  $\nu_{max}^{CHCl_3}$  3350 cm<sup>-1</sup>, 1708 cm<sup>-1</sup>. Anal. Calculated for C12H13N2SO3F3: C, 44.72; H, 4.06; N, 8.69; S, 9.95. Found: C, 44.47; H, 3.81; N, 8.95; S, 10.32.

### 4-Butyl-6-chloro-3-oxo-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide

4-Butyl-6-chloro-3-oxo-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide was obtained in 88% yield from the oily N-carbonyl chloride derivative by the above procedure. It crystallized from ether - petroleum ether and melted at 152°.  $\lambda_{\max}^{MeOH}$  252.5 m $\mu$  (11,310), 295 m $\mu$  (2,170);  $\#_{\max}^{OHCl_2}$  3350 cm<sup>-1</sup>, 1705 cm<sup>-1</sup>. Anal. Calculated for C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>SO<sub>3</sub>Cl: C, 45.75; H, 4.54; N, 9.70; S, 11.10. Found: C, 45.78; H, 4.59; N, 9.51; S, 11.12.

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## THE VINYLTRIFLUOROBORATE ANION<sup>1, 2</sup>

## S. L. STAFFORD

Recent interest in vinyl-metallic compounds in general (1), and in particular in the extent of carbon-boron  $\pi$ -bonding in vinyl-boron derivatives (2), prompted the preparation of the new vinylfluoroborate anion CH<sub>2</sub>=CHBF<sub>3</sub>-. The anion was desired in order to study the effect on carbon-boron  $\pi$ -bonding, and also as a member of a class of potentially useful compounds of which little is known, the mixed organohaloborates. Only two such anions— $(C_6H_5)_3BF^-$  (3) and  $CF_3BF_3^-$  (4)—have been characterized previously.3

A solution of 2.59 g (27.5 mmoles) of KF.2H<sub>2</sub>O dissolved in 3 ml of water was introduced into a reaction tube and 560 cc (STP) (25 mmoles) of CH<sub>2</sub>:CHBF<sub>2</sub> (prepared from  $(CH_2:CH)_4$ Sn and BF<sub>3</sub> (6)) containing a small amount of BF<sub>3</sub> was condensed onto it. The tube was sealed and placed in an ice bath for 4 hours. Volatile products were then removed under high vacuum through traps held at  $-78^{\circ}$  and  $-196^{\circ}$ . The only volatile material removed other than water was 56 cc (STP) of ethylene, collected at  $-196^\circ$ . The solid residue was extracted with boiling acetonitrile. Removal of the solvent gave 1.84 g (55% yield, based on CH2:CHBF2) of K+CH2:CHBF3-. Anal.: Required for C<sub>2</sub>H<sub>3</sub>F<sub>3</sub>BK: C, 17.9; H, 2.24; F, 42.5; B, 8.2%. Found: C, 17.6; H, 2.46; F, 44.6; B, 7.7%. The infrared spectrum (KBr disk) of the compound shows absorptions at 3067, 2967 (C—H stretch); 1623 (C=C stretch); 1422, 1294 (CH<sub>2</sub> and CH in-plane deformations);

1132, 1107 (B-C stretch); 1035 (B-F asymmetric stretch); 950-920; and 694 cm<sup>-1</sup>. The F-19 nuclear magnetic resonance spectrum, in aqueous solution, consists of a quartet centered at  $\delta_{\rm CCl_3F} = 138$  p.p.m., with  $J_{\rm B^{11}-F} = 51.8$  c.p.s. After standing in the tube for several days at room temperature, the solution was re-examined. In addition to the original quartet, a peak was observed at  $\delta_{CCl_{*}F} = 150$  p.p.m. (assignable to BF<sub>4</sub><sup>-</sup>) and there appeared to be a weak, very broad quartet centered near  $\delta_{CCl_3F} = 143$  p.p.m. (perhaps due to  $(CH_2:CH)_2BF_2$ ). This apparent disproportionation has not been studied further.

As would be expected, the  $CH_2:CHBF_3^-$  anion shows greater hydrolytic stability than does  $CH_2$ : CHBF<sub>2</sub>. Thus,  $CH_2$ : CHBF<sub>2</sub> in contact with water at room temperature gives appreciable amounts of ethylene in a few hours. Solutions containing CH<sub>2</sub>:CHBF<sub>3</sub><sup>-</sup>, on the other hand, are stable to hydrolysis for at least several days.

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The formation of organohaloborate anions by addition of hydrogen halides to amine adducts of organoboron halides has been postulated (5).