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An Improved Synthesis of *N*-(Butylaminocarbonyl)-4-hydroxymethyl-benzenesulfonamide, One of the Metabolites of Tolbutamide, and Synthesis of Its Formyl Derivative

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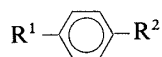
An improved synthesis of *N*-(butylaminocarbonyl)-4-hydroxymethyl-benzenesulfonamide, one of the metabolites of tolbutamide, and its transformation to the formyl derivative are described.

Keywords—tolbutamide; hydroxymethyl-tolbutamide; formyl-tolbutamide; metabolite of tolbutamide

In order to continue our studies¹⁾ aimed at developing new quantitative measurement for metabolites of tolbutamide (**1**) in biological fluids, an ample supply of *N*-(butylaminocarbonyl)-4-hydroxymethyl-benzenesulfonamide (**2**) was required for use as an authentic standard compound. Although there have been several reports¹⁻⁵⁾ concerning the synthesis of this compound, the overall yields were poor. For example, treatment of homosulfamine with nitrous acid,⁶⁾ which provided the starting material for the synthesis of **2** reported by Tagg and his co-workers, gave 4-hydroxymethyl-sulfonamide (**3**) in low yield after tedious work-up. We report here an improved synthesis of the metabolite.

Treatment of the ester (**4**)⁷⁾ with *n*-butyl isocyanate in tetrahydrofuran in the presence of potassium carbonate afforded the *N*-butylaminocarbonyl ester (**5**) in 64% yield; this was a key intermediate. Thus, hydrolysis of **5** with potassium carbonate in aqueous ethanol gave the acid (**6**), one of the metabolites of tolbutamide, in good yield. On the other hand, reduction of **5** with lithium aluminium hydride in tetrahydrofuran at -78°C for 6 h and then at 0°C overnight furnished the hydroxymethyl-tolbutamide (**2**) in 80% yield. The result obtained from the above reaction sequence was superior to those previously reported from the viewpoint of overall yield.

The improved synthesis of **2** prompted us to carry out a transformation of **2** into the formyl-tolbutamide (**7**), the latter of which has not been prepared so far, although it was



- 1**: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{SO}_2\text{NHCONHBu}^n$
2: $\text{R}^1 = \text{CH}_2\text{OH}$, $\text{R}^2 = \text{SO}_2\text{NHCONHBu}^n$
3: $\text{R}^1 = \text{CH}_2\text{OH}$, $\text{R}^2 = \text{SO}_2\text{NH}_2$
4: $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{SO}_2\text{NH}_2$
5: $\text{R}^1 = \text{CO}_2\text{Me}$, $\text{R}^2 = \text{SO}_2\text{NHCONHBu}^n$
6: $\text{R}^1 = \text{CO}_2\text{H}$, $\text{R}^2 = \text{SO}_2\text{NHCONHBu}^n$
7: $\text{R}^1 = \text{CHO}$, $\text{R}^2 = \text{SO}_2\text{NHCONHBu}^n$

Chart

suggested earlier by McDaniel and his co-workers⁸⁾ that **7** might be a plausible intermediate in the conversion of **2** to the acid (**6**). An attempt to transform the benzyl alcohol group of **2** to the formyl group with manganese dioxide in chloroform gave the formyl-tolbutamide (**7**) in poor yield. Treatment of **2** with pyridinium chlorochromate⁹⁾ in methylene chloride at room temperature overnight afforded the formyl-tolbutamide (**7**) in 75% yield. These products should be useful for more precise investigations of the metabolic pathway of tolbutamide.

Experimental

Melting points were determined with a Yanagimoto hot-stage apparatus and are uncorrected. Infrared (IR) spectra were taken with an EPI-G2 grating infrared spectrometer (Hitachi) in Nujol mull. ¹H-Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL PMR 60 or a JEOL FX 90-Q spectrometer in deuteriochloroform with tetramethylsilane as an internal standard.

Methyl 4-Butylaminocarbonylamino-sulfonylbenzoate (5)—A mixture of the ester (**4**) (4 g), *n*-butyl isocyanate (4 g), potassium carbonate (2.5 g), and tetrahydrofuran (150 ml) was heated under reflux with stirring overnight and concentrated under reduced pressure to give a residue, which was dissolved in water. The aqueous solution was washed with CHCl₃ and acidified with conc. HCl to give **5** (3.8 g), which crystallized from EtOH, mp 167–169 °C. IR ν_{\max} cm⁻¹: 3350, 1735, 1650. ¹H-NMR δ : 0.95 (3H, diffused t, *J*=5.5 Hz), 1.45 (4H, m), 3.25 (2H, q, *J*=6 Hz), 4.00 (3H, s), 6.55 (1H, br s), 7.20 (1H, br s), 7.98 (2H, q, *J*=10 Hz), 8.20 (2H, d, *J*=10 Hz). *Anal.* Calcd for C₁₃H₁₈N₂O₅S·1/3H₂O: C, 48.74; H, 5.87; N, 8.75. Found: C, 48.84; H, 5.61; N, 8.79. Mass spectrum (MS): 214 (M⁺). Hydrolysis of the foregoing ester (**5**) with potassium carbonate in aqueous EtOH gave the acid (**6**) in good yield; this product was identical with an authentic sample of the acid (**6**).

Reduction of the Ester (5) with Lithium Aluminium Hydride—A solution of the ester (**5**) (2 g) in tetrahydrofuran (30 ml) was added dropwise to a solution of lithium aluminium hydride (2 g) in tetrahydrofuran (150 ml) with stirring at -78 °C for 6 h and at 0 °C overnight. After decomposition of the excess reagent with water, the mixture was concentrated under reduced pressure to leave a residue, which was taken up in water. The aqueous solution was acidified with HCl and extracted with ethyl acetate. The extract was washed with water and dried. Removal of the solvent under reduced pressure gave a residue, which crystallized from ether-CHCl₃ to afford the hydroxymethyl-tolbutamide (**2**) (1.05 g). The mother liquor was concentrated to dryness and the residue was chromatographed on silica gel in CHCl₃ with increasing amounts of EtOH to give an additional crop of **2** (0.4 g), mp 116–118 °C, identical with an authentic sample.¹⁾

The Formyl-tolbutamide (7)—A mixture of the hydroxymethyl-tolbutamide (**2**) (500 mg), pyridinium chlorochromate (600 mg), and CH₂Cl₂ (60 ml) was stirred at 0 °C for 5 h and then at room temperature overnight. A few drops of EtOH were added to the mixture and the whole was stirred for 2 h then filtered. The filtrate was washed with aqueous sodium carbonate. The washing was acidified with HCl and extracted with CHCl₃. The organic extract was washed with water, dried and concentrated. The residue was crystallized from EtOH to give the formyl-tolbutamide (**7**) (375 mg), mp 142–143 °C, IR ν_{\max} cm⁻¹: 3350, 1700, 1650. ¹H-NMR δ : 0.95 (3H, diffused t, *J*=5.7 Hz), 1.00–1.90 (4H, m), 3.22 (2H, q, *J*=6.0 Hz), 6.50 (1H, br s), 8.05 (4H, s), 7.80–8.80 (1H, br), 10.09 (1H, s). *Anal.* Calcd for C₁₂H₁₆N₂O₄S: C, 50.69; H, 5.67; N, 9.85. Found: C, 50.96; H, 5.96; N, 9.72.

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