

Convenient Method for Synthesis of Hydroxymethylcarbamates

A convenient method for the preparation of aryl hydroxymethylcarbamate from aryl carbamates by reaction with paraformaldehyde in tetrahydrofuran and a catalytic amount of acid is reported. By using this method 1-naphthyl, phenyl, and 7-(2,2-dimethyl-2,3-dihydrobenzofuranyl) hydroxymethyl-

carbamate were prepared in 35–61% yield. Reaction with 2-methyl-2-methylthiopropionaldehyde *O*-(carbamoyl) oxime, however, failed to give the expected hydroxymethyl derivative and a dimeric condensation product was obtained instead.

Hydroxymethylcarbamate esters have been shown to be one of the principal products obtained from the metabolism of insecticidal methylcarbamate esters in insects, mammals, and plants (Dorough, 1970; Kuhr, 1970). The need for authentic samples of hydroxymethylcarbamates for the purpose of identifying metabolic products of methylcarbamates by comparison of chromatographic data has stimulated considerable effort in the synthesis of these compounds. Although several methods have been described for their synthesis, these methods often produce poor yields or require intermediates which are not readily available. For example, Dorough and Casida (1964) prepared 1-naphthyl hydroxymethylcarbamate in minute yield by prolonged reflux of a mixture of 1-naphthyl carbamate with excess paraformaldehyde in glacial acetic acid. 1-Naphthyl hydroxymethylcarbamate also has been prepared in 2% yield by synthesis of the corresponding benzyloxymethylcarbamate followed by catalytic hydrogenation (Balba *et al.*, 1968). More recently, Durden *et al.* (1970) have described a procedure which involves the preparation of (2-pyranyloxy)methylcarbamate which, in turn, affords the desired hydroxymethylcarbamate upon acid-catalyzed hydrolysis.

In the course of our studies on the derivatization of carbamate esters, we have succeeded in synthesizing conveniently and in moderate yields several aryl hydroxymethylcarbamates by simply reacting aryl carbamates with paraformaldehyde in aqueous tetrahydrofuran (THF) as the solvent and a catalytic amount of concentrated hydrochloric acid. This communication describes procedures which may be used as a general synthetic route for the preparation of aryl hydroxymethylcarbamates.

EXPERIMENTAL

Phenyl carbamate (1), mp 135–9° C, 1-naphthyl carbamate (2), mp 175–7° C, 7-(2,2-dimethyl-2,3-dihydrobenzofuranyl) carbamate (3), mp 172–4° C, and 2-methyl-2-methylthiopropionaldehyde *O*-(carbamoyl)oxime (4), mp 92–4° C, were prepared by the reaction between the appropriate chloroformate and ammonia as previously described (Strain *et al.*, 1950; Fahmy *et al.*, 1966; Payne *et al.*, 1966). Pmr spectra were obtained on a Varian T-60 spectrometer and infrared spectra on a Perkin-Elmer Model 21 recording infrared spectrophotometer.

1-Naphthyl Hydroxymethylcarbamate (5). A mixture of 5.6 g of 2 (0.03 mol), 40 ml of THF, 10 ml of water, 1.2 g of paraformaldehyde (0.04 mol), and 1.0 ml of concentrated hydrochloric acid was stirred and heated gently to 50–60° C until a clear solution was obtained. The mixture was main-

tained at this temperature for 1 hr, then allowed to stand at room temperature for another hour. Dilution of the mixture with 100 ml of water produced an oil which was separated and the aqueous layer was extracted with three 50-ml portions of ether and the extracts were combined with the oil. The ether solution was washed with water, dried over anhydrous sodium sulfate, and the ether was removed to give an oil which solidified when concentrated under vacuum. Recrystallization from benzene and hexane gave 3.8 g of 5 (59% yield), mp 134–6° C, reported 136–7° C (Durden *et al.*, 1970). Pmr spectrum in *d*₆-dimethylsulfoxide with tetramethylsilane (TMS) as an internal standard showed a 2H doublet centered at δ 4.7 ($J = 7$ Hz) for NCH₂O protons and a 7H multiplet at δ 7.25–8.22 for the aromatic protons. Infrared spectrum in Nujol oil showed a band for NH, OH at 3300 cm⁻¹, and a carbonyl band at 1705 cm⁻¹.

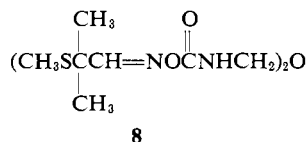
7-(2,2-Dimethyl-2,3-dihydrobenzofuranyl) Hydroxymethylcarbamate (6). This compound was prepared according to the procedure described for 5 except the reaction mixture was neutralized with sodium carbonate at the end of the heating period and the THF solvent was removed under reduced pressure. Extraction of the residual product in chloroform, removal of the chloroform, and recrystallization from benzene-hexane gave 6 in 61% yield, mp 130–3° C, reported 131–3° C (Metcalf *et al.*, 1968). Pmr (*d*₆-dimethylsulfoxide–TMS) spectrum showed a 3H multiplet at δ 6.7–7.2 for aromatic protons, 1H triplet centered at δ 5.7 for the NH proton, 2H multiplet at δ 4.4–4.7 for NCH₂O, 2H singlet at δ 3.1 for the furanyl methylene protons, and a 6H singlet at δ 1.4 for furanyl *gem*-dimethyl protons. Infrared spectrum in Nujol oil showed a band for NH, OH at 3300 cm⁻¹, and a carbonyl band at 1725 cm⁻¹.

Phenyl Hydroxymethylcarbamate (7). This compound was prepared by the procedure used for 6 in 35% yield after recrystallization from benzene-hexane, mp 93–6° C. Pmr (*d*-chloroform–TMS) spectrum showed a 5H multiplet at δ 7.0–7.65 for aromatic protons, a broad signal 1H at δ 6.0–6.5 for NH proton, and a 2H doublet centered at δ 4.8 ($J = 7$ Hz) for NCH₂O protons. Infrared spectrum in Nujol oil showed two bands for NH, OH at 3280 cm⁻¹ and 3350 cm⁻¹, and a carbonyl band at 1700 cm⁻¹.

Anal. Calcd for C₈H₉O₃N: C, 57.49; H, 5.39; N, 8.38. Found: C, 57.24; H, 5.43; N, 8.90.

Reaction of 4 with Paraformaldehyde in THF. A mixture of 3.0 g of 4, 1.0 g of paraformaldehyde, 50 ml of THF, and two drops of concentrated hydrochloric acid was heated at reflux for 4 hr and then neutralized with sodium carbonate. The solvent was removed under reduced pressure, the residue

taken up in 50 ml of boiling carbon tetrachloride, 0.5 g of charcoal added, and the hot mixture was filtered. Addition of hexane to the filtrate produced 0.9 g of a crystalline solid, mp 152-4° C (dec). Pmr (*d*-chloroform-TMS) spectrum of this substance showed a 1H singlet at δ 7.5 for —CH=N proton, 1H multiplet at δ 7.3-7.6 for NH proton, 2H doublet centered at δ 4.5 ($J = 6.0$ Hz) for NCH₂O protons, 3H singlet at δ 1.95 for CH₃S protons, and a 6H singlet at δ 1.45 for *gem*-dimethyl protons. Infrared spectrum in Nujol oil showed a band for NH at 3320 cm⁻¹ and a carbonyl band at 1715 cm⁻¹. Elemental analysis, pmr data, and infrared spectrum were consistent with the structure below.



Evidently, **8** is formed by the condensation of two molecules of the desired hydroxymethylcarbamate with the elimination of a molecule of water.

Anal. Calcd for C₁₄H₂₈N₄O₅S₂: C, 42.63; H, 6.60; N, 14.21. Found: C, 42.74; H, 6.58; N, 13.98.

2-Methyl-2-methylthiopropionaldehyde *O*-(hydroxymethylcarbamoyl) oxime reported by Durden *et al.* (1970) differed from **8** in melting point (83-4° C) and in the chemical shifts for the NH and NCH₂O protons. Additional experiments in which **4**, paraformaldehyde, and a trace of hydrochloric acid were allowed to stand at room temperature or when gaseous monomeric formaldehyde was passed into a THF solution of **4** containing hydrochloric acid at room temperature returned only starting materials upon workup. However, heating the reaction mixture resulted mainly in **8**, unchanged

4, and minor amounts of unidentified materials as products. These results suggest that at elevated temperatures the rate of reaction between **4** and formaldehyde is slower than the rate of formation of **8** from **4**, and consequently **8** is the principal product isolated. Thus, it appears that the procedures described above are not applicable for the preparation of the hydroxymethyl derivative of aldicarb, an oxime carbamate. The method, however, should have general applicability for the synthesis of aryl hydroxymethylcarbamates.

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