apparently altered, causing an increase in the rate of absorption as the hydrogen-ion activity becomes less. The nature of this alteration could be a change in the membrane pore size or some other structural change in the membrane.

The extremes of the pH range used in this study are not harmful to either of the fish which may live for extended periods at either pH 5.0 or 9.0. Further, it is doubtful that the changes in pH have interfered with the integrity of the membrane. The possibility of a synergistic toxicity of the hydrogen ion–ethanol combination, independent of absorption rate, could not be ruled out. Preliminary experiments on guppies with strychnine, however, showed a similar increase in absorption rate at high pH levels. The observed absorption rate increase was considerably greater than that accounted for by calculation of the amount of strychnine present as the free base at elevated pH levels.

Results from this study indicate that the absorbing membranes of the guppies are pH sensitive. The use of this fish as an experimental model in studying drug absorption probably should be limited to those studies in which the pH of the solutions used is constant. Absorption studies that are run with pH as a variable factor probably will be influenced by the changing absorption rates due to varying pH, and any change in absorption rate in such a study may not be meaningful. Goldfish, on the other hand, appear to have absorbing membranes which are not appreciably altered by pH changes *per se*.

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*Keyphrases*

Absorption of ethanol
pH dependence of absorption rate in guppies
pH independence of absorption rate in goldfish
Membrane sensitivity to pH

# Mixed Glycol Acetal Dimethylcarbamates *via* Transacetalation of Certain Di- and Trihydric Alcohols

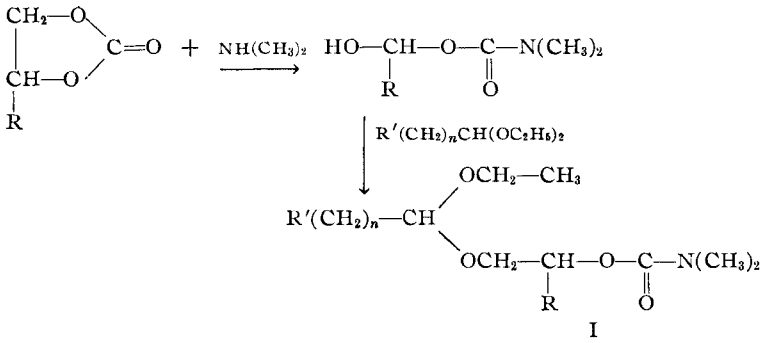
By CLAUDE PIANTADOSI, FRED T. SEMENIUK, and ROBERT K. RAUCH

**Mixed acetals of a new type were synthesized by an acetal exchange reaction between the mono dimethylcarbamate of ethylene, propylene, and trimethylene glycols and the diethyl acetals of butyraldehyde, heptaldehyde, and benzaldehyde. The glycerol carbonate (followed by dimethylaminolysis) also underwent transacetalation and dimethylcarbamate esters of the dioxolane-type were synthesized.**

A NUMBER of acyclic acetals (1), cyclic acetals (2), and their derivatives (3–9) have been reported in the literature. Their potentialities as hypnotics, anticonvulsants, and skeletal muscle relaxants (3–9) have been noted. In view of the fact that mixed acetals are similar in structure to the pharmacologically active glycerol ethers, it was of interest to synthesize some of the mixed acetal carbamates in order to determine the feasibility of the transacetalation reaction for preparing such compounds. Exchange reactions between alcohols in acetal linkage and alcohols have long been known. They have been reported to be applicable for primary alcohols (10, 11), for secondary and tertiary alcohols and phenols (11), for ethylene and trimethylene glycol (12), and for glycerol (13–15). The term "transacetalation" has been coined and may be applied generally to cover all such acetal exchange reactions (13). The experimental procedures presented in this paper describe the use of this reaction with the glycol monocarbamates of ethylene, propylene, trimethylene, and glycerol with the diethyl acetals of benzaldehyde, butyraldehyde, and heptaldehyde. Attempts to prepare the unsubstituted carbamate derivatives by this method were not successful.

The diethyl acetals of butyraldehyde, heptaldehyde, and benzaldehyde were prepared according to the method of Claisen (16). The method of Najer *et al.* (17) was used for the preparation of propylene glycol carbonate and the method of Carothers *et al.* (18) for trimethylene glycol carbonate. An adaptation of the method of Delaby *et al.* (19) for the synthesis of ethylene glycol monocarbamate was used in preparing the carbamates. The synthesis of heptaldehyde and benzaldehyde mixed glycerol carbonate acetals and dioxolane dimethylcarbamates were carried out as previously described by Piantadosi *et al.* (13). An examination of the infrared spectrum of the compounds synthesized revealed the presence of characteristic ester absorption due to C=O stretching in the region of 1620–1829

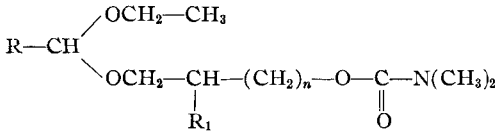
Received April 25, 1967, from the School of Pharmacy, University of North Carolina, Chapel Hill, NC 27514
Accepted for publication August 3, 1967.
Presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, Dallas meeting, April 1966.
The authors acknowledge the assistance of Dr. E. O. Oswald and John C. Cavallito in the preparation of intermediates.



R = H or $CH_3$, R′ = aliphatic or aromatic. $n$ = 0, 1, 2, 5

*Scheme I*

TABLE I—MIXED ACETAL DIMETHYLCARBAMATES



| R | $R_1$ | $n$ | Formula | Yield, % | B.p., °C. (mm.) | Anal., % C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_3H_7$ | H | 0 | $C_{11}H_{23}NO_4$ | 60 | 83 (0.3) | 56.63 | 56.87 | 9.94 | 10.04 | 6.01 | 5.89 |
| $C_6H_5$ | H | 0 | $C_{14}H_{21}NO_4$ | 66 | 122 (0.3) | 62.90 | 63.19 | 7.92 | 7.88 | 5.24 | 5.25 |
| $C_6H_{13}$ | H | 0 | $C_{14}H_{29}NO_4$[a] | 54 | 108 (0.3) | 61.06 | 61.58 | 10.61 | 10.32 | 5.09 | 5.30 |
| $C_6H_5$ | $CH_3$ | 0 | $C_{15}H_{23}NO_4$ | 57 | 122 (0.4) | 64.03 | 64.22 | 8.24 | 8.39 | 4.98 | 5.10 |
| $C_3H_7$ | $CH_3$ | 0 | $C_{12}H_{25}NO_4$ | 49 | 80 (0.4) | 58.27 | 58.49 | 10.19 | 10.42 | 5.66 | 5.76 |
| $C_6H_{13}$ | $CH_3$ | 0 | $C_{15}H_{31}NO_4$ | 60 | 110 (0.4) | 62.25 | 62.04 | 10.80 | 10.84 | 4.84 | 4.88 |
| $C_3H_7$ | H | 1 | $C_{12}H_{25}NO_4$ | 57 | 93 (0.3) | 58.27 | 58.78 | 10.19 | 10.00 | 5.66 | 5.56 |
| $C_6H_5$ | H | 1 | $C_{15}H_{23}NO_4$ | 43 | 124 (0.2) | 64.03 | 64.66 | 8.24 | 8.36 | 4.98 | 4.85 |
| $C_6H_{13}$ | H | 1 | $C_{15}H_{31}NO_4$[b] | 50 | 108 (0.3) | 62.25 | 62.24 | 10.80 | 10.99 | 4.84 | 4.95 |

[a] 2-(1-Ethoxyheptoxy)ethyl benzoate was prepared in the usual manner, b.p. 39° (0.3). Calcd. for $C_{18}H_{28}O_4$: C, 70.08; H, 9.15. Found: C, 70.29; H, 9.50. [b] 3-(1-Ethoxyheptoxy)propyl benzoate was prepared, b.p. 52° (0.4). Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.34; H, 9.61.

cm.$^{-1}$ and the C—O—C bands at 1050–1275 cm.$^{-1}$. Scheme I for the synthesis of 3-(1-ethoxybutoxy) propyl dimethylcarbamate(I) illustrates the reaction sequence for the preparation of mixed acetal dimethylcarbamates. Data with respect to these derivatives are listed in Table I. Scheme II depicts the route used in the synthesis of dioxolane carbamates (*Va*) and mixed glycerol carbamate acetals (IV*b*).

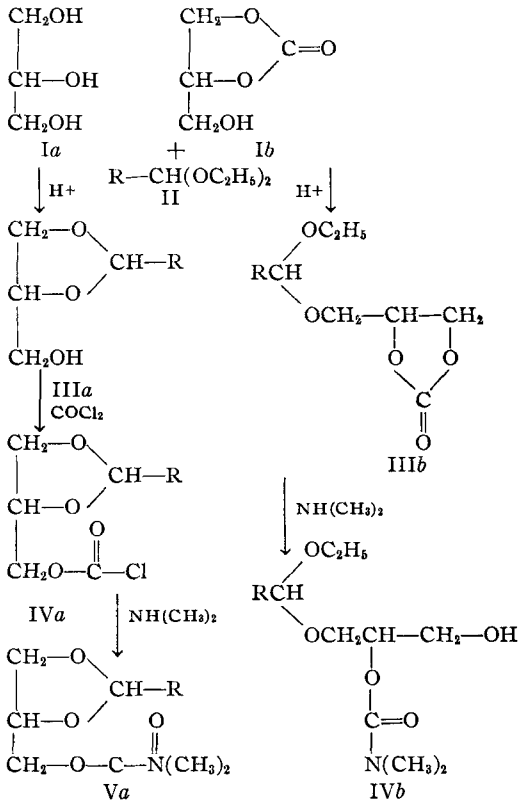
## EXPERIMENTAL

All boiling points and melting points are uncorrected. Analyses were determined by Weiler and Strauss Microanalytical Laboratory, Oxford, England, Spang Microanalytical Laboratory, Ann Arbor, Mich., and M-H-W Laboratories, Garden City, Mich. Infrared spectra were recorded with a Perkin-Elmer Infracord.

**3-(1-Ethoxybutoxy)propyl Dimethylcarbamate (I)**—The following procedure is based on a modification of the method of Alquier (20) and subsequently of others (15). This method was used for all the products obtained from ethylene, propylene, and trimethylene glycols. Table I indicates pertinent data with respect to the mixed acetal dimethylcarbamates synthesized.

In a three-necked flask equipped with a stirrer, a thermometer, and a distilling head for the collection of the alcohol evolved, were placed 13.3 Gm. (0.1 mole) of ethylene glycol monodimethylcarbamate and 58.4 Gm. (0.4 mole) of butyraldehyde diethyl acetal. The reaction mixture was heated with vigorous stirring on an oil bath. When the temperature of the reaction mixture reached 115°, a drop of concentrated HCl was added, and ethanol began to evolve. After the theoretical amount of ethanol was obtained, the reaction mixture was cooled, and 50 ml. of ether was added. The ethereal solution was washed once with 30 ml. of saturated $NaHCO_3$, and three times with 30-ml. portions of cold water. The ether extract was dried over anhydrous sodium sulfate and the ether was removed under reduced pressure. The resulting product was purified by distillation under reduced pressure. Compounds listed in Table I were prepared in an analogous manner.

**4 - Hydroxymethyl - 2 - n - hexyl - 1,3 - dioxolane Dimethylcarbamate (Va)**—To 37.6 Gm. (0.2 mole) of 4-hydroxymethyl-2-*n*-hexyl-1,3-dioxolane dissolved in 80 ml. of benzene was added dropwise 0.2 mole of phosgene. The mixture was stirred for 3 hr. at which time 0.2 mole of dimethylaniline was added. Stirring was maintained for another 30 min. and the mixture was washed with ice water. A separation of benzene and water layers occurred, and the benzene layer was poured into 150 ml. of a 25% aqueous solu-




*Scheme II*

tion of dimethylamine. The reaction mixture was placed in an ice bath and stirred for 3 hr. The benzene layer was separated, dried over anhydrous potassium carbonate, and removed by evaporation. The residue was purified by distillation under reduced pressure, b.p. 106–107° (0.14 mm.); $n_D^{25}$ 1.4517.

*Anal.*—Calcd. for $C_{13}H_{25}NO_4$: C, 60.20; H, 9.72; N, 5.40. Found: C, 60.76; H, 9.54; N, 5.46.

In a similar manner the benzaldehyde analog was prepared. After evaporation of the benzene, distillation of the residue under vacuum afforded 12.8 Gm. of a yellow colored liquid, b.p. 140° (0.14 mm.); $n_D^{25}$ 1.5180. Upon standing in the cold (5°), approximately 1 Gm. of white crystals was collected from this liquid fraction, m.p. 115–116°. Both liquid and solid were submitted for analyses.

*Anal.*—Calcd. for $C_{13}H_{17}NO_4$: C, 63.13; H, 6.82; N, 5.58. Found: (solid) C, 63.23; H, 6.88; N, 5.26. (Liquid): C, 63.26; H, 6.66; N, 5.36.

**Mixed Glycerol Carbamate Acetals (IVb)**—To 11.8 Gm. (0.1 mole) of freshly distilled glycerol carbonate was added 75.2 Gm. (0.4 mole) of heptaldehyde diethyl acetal. The reaction mixture was heated to 150° and two drops of concentrated HCl was added. After cooling, ether was added, followed by neutralization with a weak base. The mixture was then washed with water, and the organic layer was dried over anhydrous potassium carbonate and subsequently removed by evaporation. Distillation of the residue gave a product (III*b*) with b.p. 147° (0.23 mm.); $n_D^{27}$ 1.4444.

*Anal.*—Calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.78; H, 9.17.

Similarly, the corresponding benzaldehyde derivative was obtained, b.p. 155–157° (0.14mm.); $n_D^{27}$ 1.5079.

*Anal.*—Calcd. for $C_{13}H_{15}O_5$: C, 61.89; H, 6.39. Found: C, 62.03; H, 6.35.

To obtain the carbamate (IV*b*) 0.1 mole of III*b* was placed in 100 ml. of a 25% aqueous solution of dimethylamine. The mixture was set aside for 4 days, and the layers separated and distilled, b.p. 143° (0.15 mm.); $n_D^{25}$ 1.4488.

*Anal.*—Calcd. for $C_{15}H_{31}NO_5$: C, 58.99; H, 10.23; N, 4.59. Found: C, 59.07; H, 10.06; N, 4.50.

The corresponding benzaldehyde derivative was obtained as a viscous yellowish-brown liquid. This oil was purified in a molecular still, b.p. 160° (0.13 mm.); $n_D^{25}$ 1.5020.

*Anal.*—Calcd. for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 61.00; H, 8.03; N, 4.59.

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*Keyphrases*

Glycol acetal dimethylcarbamates
Glycol acetal dimethylcarbamates—synthesis
Transacetalation of di- and trihydric alcohols
IR spectrophotometry—structure