Thin-Layer Chromatography—Thin-layer plates (5 × 20 cm.) made of silica gel G were used. Van Urk's reagent (6) was used as a spray reagent to differentiate the starting material and product by a varied color response.

Spectra—UV spectra were obtained on a Beckman DK 2 spectrophotometer (1-cm. cell) in methylene chloride as solvent. IR spectra were determined on a Beckman IR 8 spectrophotometer in potassium bromide pellets and methylene chloride liquid films. NMR spectra were determined on a Varian 60 MC spectrophotometer using deuterochloroform as the solvent and tetramethylsilane as the internal standard.

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New Compounds: Demethylated Methocarbamol

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Abstract □ Two isomeric monocarbamates of 3-(*o*-benzyloxyphenoxy)-1,2-dihydroxypropane and 3-(*o*-hydroxyphenoxy)-1,2-dihydroxypropane were synthesized. The structural assignments are supported by spectral data.

Keyphrases □ Demethylated methocarbamol derivatives—synthesis, structure determination □ Methocarbamol metabolites—synthesis, structure determination □ NMR spectroscopy—structure, identification

Baizer *et al.* (1) have presented rigorous proof of the structure of some isomeric monocarbamates of 1,2-dihydroxy-3-aryloxypropanes by independent unequivocal synthesis. In a later paper, Swidinsky *et al.* (2) reported the preparation of two isomeric monocarbamates of 3-(*o*-hydroxyphenoxy)-1,2-dihydroxypropane, Compounds III and IV, by catalytic debenzylation of Compounds I and II. However, their tentative structural assignments differ from those reported here.

This work was prompted by a need for one of the metabolites (Compound III) of methocarbamol.[1] It is shown that the isomeric monocarbamates can be identified by spectral data. The results of a single run indicate that the major product of the reaction of ammonia with the cyclic carbonate, 4-(*o*-benzyloxyphenoxymethyl)-1,3-dioxolone-2, is a primary carbamate (Compound I) and the minor product is a secondary carbamate (Compound II). The isomeric compounds and their melting-point values are shown in Table I.

The NMR spectra of the isomeric pairs (I, II and III, IV) taken in dimethyl sulfoxide-d_6 exhibit significant and distinguishing differences. Compound II clearly must have the secondary carbamate structure as shown by the splitting of the primary hydroxyl proton into a triplet (δ 4.90; J = 5.5 cps.)[2] by the adjacent methylene group, rather than a doublet as expected for a secondary hydroxyl proton. In addition, the methylene protons, CH_2OH, adjacent to the hydroxyl group are coupled by approximately the same coupling constant (5.5 cps.) to the OH proton and the adjacent methine hydrogen, giving rise to a triplet (δ 3.67) which collapses to a doublet on deuteration.

The isomeric Compound I in dimethyl sulfoxide-d_6 shows only a single unsplit hydroxyl peak[3] with all five aliphatic hydrogens appearing under a broad distorted doublet centered at δ 4.1. Acetylation of the hydroxyl group, however, shifts the secondary methine absorption approximately 1.3 p.p.m. down-field,[4] supporting the primary carbamate structure for Compound I.

The NMR structural assignments are supported by the fact that the comparable features of the spectra of I and II are nearly identical to those of the related analogs of known structure (1), 3-(*o*-methoxyphenoxy)-2-hydroxy-1-propyl carbamate and 3-(*o*-methoxyphenoxy)-1-hydroxy-2-propyl carbamate, respectively.

EXPERIMENTAL[5]

The method of Swidinsky *et al.* (2) was used for the preparation of 4-(*o*-benzyloxyphenoxymethyl)-1,3-dioxolone-2.

3-(*o*-Benzyloxyphenoxy)-2-hydroxy-1-propyl Carbamate (I)—While maintaining a reaction temperature below 40°, a suspension of 4-(*o*-benzyloxyphenoxymethyl)-1,3-dioxolone-2 (74 g., 0.25 mole) in isopropyl alcohol (800 ml.) was saturated with ammonia. The mixture was allowed to stand at ambient temperatures for 24 hr.

[1] Methocarbamol is marketed as Robaxin by A. H. Robins Co., Inc., Richmond, Va.

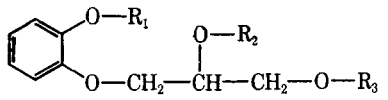
[2] The OH absorption is superimposed on the methine multiplet but is clearly distinguishable and easily removed by deuteration.

[3] Evidently the exchange rate is too great in this case for splitting to be seen.

[4] This comparison was made using $CDCl_3$ as the solvent for both the acetylated and nonacetylated samples.

[5] Melting points are corrected. Elemental analyses were performed by the Analytical Department, Research Laboratories, A. H. Robins Co., Inc., Richmond, Va.

Table I—Isomeric Monocarbamates



No.	R_1	R_2	R_3	M.p.	Anal., % Calcd.	Found
I	$-CH_2C_6H_5$	—H	$-CONH_2$	85–88° (86.6–87.6°[a])	C, 64.34 H, 6.03 N, 4.41	C, 64.17 H, 6.01 N, 4.42
II	$-CH_2C_6H_5$	$-CONH_2$	—H	100–102.5° (73.6–74.8°[b])	C, 64.34 H, 6.03 N, 4.41	C, 64.21 H, 5.97 N, 4.43
III	—H	—H	$-CONH_2$	124–128° (125–126°[c])	C, 52.86 H, 5.77 N, 6.16	C, 52.68 H, 5.81 N, 6.07
IV	—H	$-CONH_2$	—H	94–100° (116–118°[d])	C, 52.86 H, 5.77 N, 6.16	C, 52.69 H, 5.71 N, 6.16
V	$-CH_2C_6H_5$	$-COCH_3$	$-CONH_2$	60–67°	C, 63.50 H, 5.89 N, 3.90	C, 63.12 H, 5.85 N, 3.79

[a] This melting point was reported (2) for Structure II. [b] This melting point was reported (2) for Structure I. [c] This melting point was reported (2) for Structure IV. [d] This melting point was reported (2) for Structure III.

and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate with the aid of activated charcoal, yield 49 g. (61.5%).

A sample of the acetate derivative, Compound V, was prepared for NMR analysis by refluxing a mixture of 0.5 g. of I, 20 ml. of acetic anhydride, and 0.5 g. of sodium acetate for 1 hr. After workup, the product was recrystallized from isopropyl ether, yield 0.3 g.

3-(*o*-Benzyloxyphenoxy)-1-hydroxy-2-propyl Carbamate (II)—The filtrate from the preparation of Compound I was concentrated to about two-thirds volume and refrigerated. The crystals were filtered and recrystallized twice from ethyl acetate, 3.5 g. (4.5%). TLC (eluted with 10% methanol in chloroform) indicated a single component different from Compound I.

3-(*o*-Hydroxyphenoxy)-2-hydroxypropyl Carbamate (III)—A solution of Compound I (12.6 g., 0.04 mole) in absolute ethanol (200 ml.) containing about 1 g. of palladium-on-charcoal (10%) was subjected to Parr hydrogenation at ambient temperature. The theoretical amount of hydrogen was absorbed during 10 min. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized twice from ethyl acetate, yield 2.8 g. (31%).

1-Hydroxymethyl-2-(*o*-hydroxyphenoxy)ethyl Carbamate (IV)—The procedure followed was the same as that with Compound III. The product from 2.7 g. of Compound II was recrystallized twice from ethyl acetate, yield 0.2 g. (11%).

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