# Synthesis of *N*-Phenyl-4-hydroxyphenyl Carbamate

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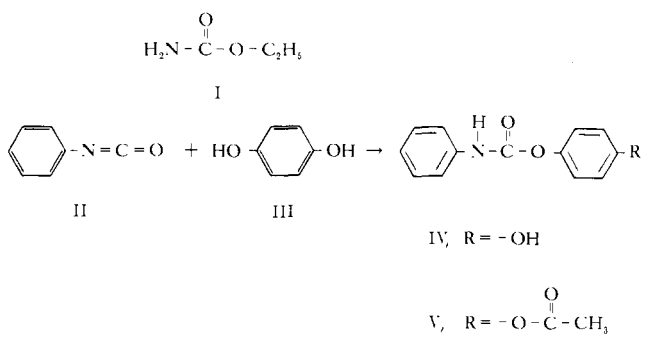
**The reaction of phenylisocyanate with an excess of hydroquinone yielded *N*-phenyl-4-hydroxyphenyl carbamate, which was isolated by column chromatography of the reaction product on silica gel. The monoacetate, *N*-phenyl-4-acetoxyphenyl carbamate, was also prepared.**

ETHYL CARBAMATE (urethane) (I) is a potent tumor-initiating agent, and phenol is a weak tumor-promoting agent for mouse skin (*1*, *2*). [The terms "initiation" and "promotion" as related to chemical carcinogenesis are defined by Van Duuren (*1*).] In our studies on the relationship between chemical structure and carcinogenic activity, we synthesized *N*-phenyl-4-hydroxyphenyl carbamate (IV) from phenylisocyanate (II) and hydroquinone (III). Compound IV satisfied our objective of combining into one molecule the carbamate and phenol moieties in order to test such compounds for carcinogenic activity.




Compound II was made to react with an excess of III in pyridine, and the solid product was chromatographed on a column of silica gel to yield a white crystalline solid, IV. The solid was identified as IV from its infrared spectrum, TLC staining characteristics, elemental analysis, and the preparation of a monoacetate *N*-phenyl-4-acetoxyphenyl carbamate (V). Compounds IV and V have not been previously prepared. The results of biological tests with these compounds will be reported elsewhere.

## EXPERIMENTAL

**N-Phenyl-4-hydroxyphenyl Carbamate, IV.** Compound II (80.0 grams, 0.67 mole) was added with stirring to 188.8 grams (1.72 moles) of III dissolved in 572 ml. of pyridine. Heat was evolved during the mixing process and the final solution was kept at room temperature for 55 minutes and then poured into 3 liters of distilled water. Water was decanted from a viscous oil which formed, and the residue was washed with six successive 750-ml. portions of distilled water. The pink solid residue was filtered and air-dried (112 grams, m.p. 155–80°). This material was mixed with 300 ml. of benzene and 75 ml. of methanol and charged into a column (60 × 4.0 cm.) of 385 grams of silica gel (0.02 to 0.5 mm.). The solvent mixture was allowed to drain from the column. The column was then eluted with 100 ml. of benzene-acetone 1%, and benzene-acetone 2%, respectively, and IV was then eluted from the column with benzene-acetone 3% (1500 ml.) and benzene-acetone 5% (300 ml.). The white solids remaining after evaporation of solvents were combined and recrystallized from chloroform-methanol and then acetone-hexane to yield white crystals [39 grams (25% yield), m.p. 164–65°]. Silica gel G TLC of IV with chloroform-methanol, 9 to 1 as solvent gave a single spot of $R_f$ 0.59 [yellow when sprayed with 0.2% $KMnO_4$ in 5% $K_2CO_3$; blue when sprayed in succession with 7% $FeCl_3$ and 5% $K_3Fe(CN)_6$, a positive test for phenols]. Infrared spectrum (KBr pellet): 3380-3290 (S) (doublet) (—OH and —NH—), 3150 (W), 3100 (W), 1750 (S)(C=O), 1615 (S), 1560 (S), 1505 (S), 1440 (S), 1320 (S), 1225 (S), 1195 (S), 1090 (M), 1085 (M), 1038 (M), 1020 (S), 1000 (M), 900 (M), 855 (M), 820 (W), 755 (S), and 690 cm.$^{-1}$ (S). Ultraviolet spectrum (95% ethanol): $\lambda_{max}$ 274 mμ ($\epsilon$ = 4000); $\lambda_{min}$, 260 mμ ($\epsilon$ = 3100).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.25; H, 4.84; N, 6.34.

**N-Phenyl-4-acetoxyphenyl Carbamate, V.** Compound IV (1.0 gram) was dissolved in 25 ml. of acetic anhydride, 1.5 grams of anhydrous sodium acetate was added, and the suspension allowed to stand at room temperature for 60 hours. The mixture was poured into 150 ml. of distilled water. A colorless oil settled to the bottom, the water was decanted, and two successive washings with 150-ml. portions of distilled water converted the oil into a white solid which was collected, dried, and recrystallized from hexane-benzene to yield white crystals [585 mg. (50% yield), m.p. 141–42°]. Infrared spectrum (KBr pellet) 3420 (sh), 3350 (—NH—), 1770 (C=O), and 1750 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.33; H, 4.86; N, 5.15.

## LITERATURE CITED

(1) Homburger, F., Ed., Van Duuren, B.L., in *Progr. Exptl. Tumor Res.* 11, 31 (1969).
(2) Van Duuren, B.L., Sivak, A., Langseth, L., Goldschmidt, B.M., Segal, A., *Natl. Cancer Inst. Monograph* **28**, 173 (1968).

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