

over anhydrous potassium carbonate and the ether then evaporated on a steam bath. The residue was dissolved in benzene and chromatographed on a column of Woelm, grade 1, neutral alumina (10 Gm., column 1 cm. \times 6 cm.) using benzene as the solvent. A single compound was obtained in the eluate. The NMR data (CDCl_3) indicated τ 7.46, 7.76 (*N*-methyl), 6.12, 6.29, 6.41, and 6.87 (*O*-methyl), and was identified with that of *O,O*-dimethylbamegine.

***O,O*-Diethyl Ether.**—A 0.1-Gm. sample of the phenolic base was dissolved in 10 ml. of methanol and added to an ethereal solution of diazoethane which was made from 7 Gm. of nitrosoethylurea and 40 Gm. of 50% potassium hydroxide solution. After standing 4 days at room temperature, the solution was treated by the usual method and the

residue crystallized from acetone as colorless rosette crystals (0.098 Gm.), m.p. 203–204°. The NMR spectrum (CDCl_3) showed τ values at 7.39, 7.71 (*N*-methyl), 6.22, and 6.40 (*O*-methyl). The NMR spectrum was superimposable with that of known *O,O*-diethylbamegine.

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Tosylation of *N*-Phenyl-*N'*-(3-hydroxypropyl)urea

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Two unexpected products, *N*-phenyl-*N'*-(3-chloropropyl)urea (II) and 2-phenylimino-2,4,5,6-tetrahydro-1,3-oxazine (III), are formed from the reaction of *p*-toluenesulfonyl chloride and *N*-phenyl-*N'*-(3-hydroxypropyl)urea (I).

AS PART of a program dealing with the synthesis of potential antiradiation drugs, it became necessary to carry out the reaction of *p*-toluenesulfonyl chloride and *N*-phenyl-*N'*-(3-hydroxypropyl)urea (I). The authors have found that this reaction in pyridine solvent gives 2 unexpected products: *N*-phenyl-*N'*-(3-chloropropyl)urea (II) and 2-phenylimino-2,4,5,6-tetrahydro-1,3-oxazine (III) in total yield of 86%.

Addition at 0–10° of an equivalent of *p*-toluenesulfonyl chloride to the hydroxypropyl urea (I) (prepared from 2 equivalents of phenyl isocyanate with 3-aminopropanol and subsequent basic hydrolysis of the product),¹ followed by acidification gave a white solid. The infrared spectrum of the solid revealed a tosylate ester band at 1340 cm^{-1} (2), and was totally void of tosylate anion absorp-

tion. When dried in a vacuum oven at 55° or allowed to stand at room temperature for 3 days, the solid decomposed. The resulting syrup did not crystallize on cooling, and its infrared spectrum showed intense tosylate anion bands at 1005 and 1020 cm^{-1} (3). When dissolved in a minimum of ethanol and poured into water, a white solid precipitated; its infrared spectrum did not show tosylate anion bands. A sodium fusion of this material revealed the presence of chlorine, and elemental analysis for C, H, N, and Cl agreed with that calculated for *N*-phenyl-*N'*-(3-chloropropyl)urea. The yield was 48%.

The conversion of —OH to —Cl during a tosylation reaction is not unprecedented. Under certain conditions and with phenols bearing nitro groups in the nucleus, an abnormal reaction (4, 5) takes place in which the OH group is replaced by chlorine.

The filtrate from the chloro-urea was made strongly basic with 10% sodium hydroxide, and additional white solid precipitated. Again, the infrared spectrum was void of tosylate anion bands. A sodium fusion for sulfur and chlorine was negative and elemental analysis agreed with that calculated for 2-phenylimino-2,4,5,6-tetrahydro-1,3-oxazine. The yield was 38%.

These observations can be rationalized in the following way. The tosylation reaction gives a mixture of the chloro-urea (II) and *N*-phenyl-

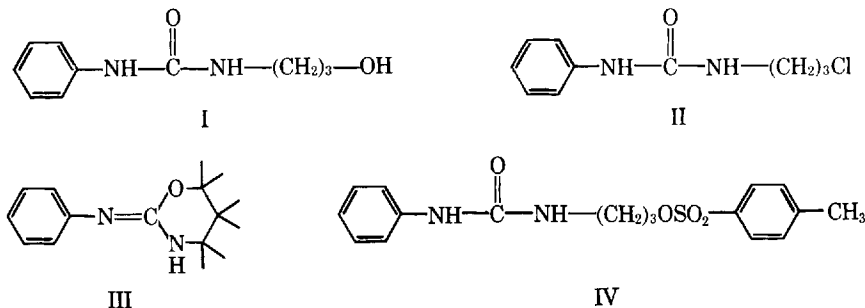
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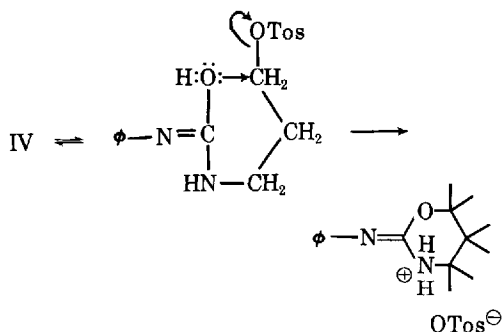
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* Deceased.

¹ The procedure used for the tosylation reaction was essentially that of Marvel and Sekera (1).



N'-(3-*p*-toluenesulfonyloxypropyl)urea (IV). Such a mixture would explain the lack of tosylate anion absorption in the infrared spectrum of the crude reaction product. On standing or warming in a vacuum oven, the tosylate ester (IV) undergoes cyclization to the oxazine salt as illustrated, thus accounting for the intense tosylate anion bands in the infrared spectrum of the decomposed material. (Scheme I.)



Scheme I

When dissolved in ethanol and poured into water, the insoluble chloro-urea precipitates and the soluble oxazine salt remains in solution. On basification of the filtrate, the free base is liberated from its salt and precipitates.

EXPERIMENTAL²

The *N*-phenyl-*N'*-(3-*N*-phenylcarbamoylpropyl)urea was prepared by the method of Dyer and Read (6).

***N*-Phenyl-*N'*-(3-hydroxypropyl)urea (I).**—To a solution of 117.4 Gm. (0.375 mole) of *N*-phenyl-*N'*-(3-*N*-phenylcarbamoylpropyl)urea in 700 ml. of 95% ethanol was added a solution of 60.0 Gm. (1.5 moles) of sodium hydroxide in 200 ml. of water. The resulting solution was refluxed for 14 hr. with mechanical stirring. A solid (sodium carbonate) separated during the reflux period. The ethanol was removed under reduced pressure, and 500 ml. of water was added to the residue. An oil (aniline) and some solid separated. The mixture was made acid (pH 3–4) by the cautious addition of hydrochloric acid with cooling and stirring. The oil disappeared (aniline hydrochloride was formed) and carbon dioxide evolved. A tan solid separated and was recovered and dried. The yield was 56.0

Gm. (77%), m.p. 106–112°. After 2 recrystallizations from acetonitrile, the compound gave a m.p. 111–113°. This sample was identical to the *N*-phenyl-*N'*-(3-hydroxypropyl)urea prepared by the method of Dyer and Read (6) from phenyl isocyanate and 3-aminopropanol.

***N*-(3-Chloropropyl)-*N'*-phenylurea (II) and 2-Phenylimino-2,4,5,6-tetrahydro-1,3-oxazine (III).**—To a solution of 46.0 Gm. (0.237 mole) of *N*-phenyl-*N'*-(3-hydroxypropyl)urea in 127.5 Gm. (1.61 moles) of pyridine was added 50.5 Gm. (0.266 mole) of *p*-toluenesulfonyl chloride. The acid chloride was added in portions, with stirring and cooling, keeping the temperature below 20°. After the addition was complete, the reaction mixture was stirred at 20° or less for 4 hr. A solution of 240 ml. of concentrated hydrochloric acid dissolved in 560 ml. of water was then added with stirring. The temperature was kept below 30°. White solid separated and, after recovery and drying *in vacuo* at room temperature, it amounted to 87.6 Gm., m.p. 84–86°. The solid was then heated *in vacuo* at 50–60° for about 1 hr. It melted³ and did not solidify on cooling. The syrup was taken up in 125 ml. of warm 95% ethanol and poured into about 1 L. of ice and water. White solid separated which, after drying, amounted to 24.3 Gm. (48%) of 1-(3-chloropropyl)-3-phenylurea (II), m.p. 115.5–121°. Three recrystallizations from acetonitrile afforded an analytical sample, m.p. 128–129.5°.

The filtrate from the chloro-urea was made strongly basic with 10% sodium hydroxide. The solid which separated was recovered and dried *in vacuo*. It amounted to 15.7 Gm. (38%) of 2-phenylimino-2,4,5,6-tetrahydro-1,3-oxazine (III), m.p. 131–134°. Two recrystallizations from acetone gave an analytical sample, m.p. 132–133.5°.

Anal.—(II) Calcd. for C₁₀H₁₃ClN₂O: C, 56.47; H, 6.16; Cl, 16.67; N, 13.17. Found: C, 56.60; H, 6.27; Cl, 16.41; N, 13.01.

Anal.—(III) Calcd. for C₁₀H₁₂N₂O: C, 68.15; H, 6.87; N, 15.90. Found: C, 68.16; H, 6.90; N, 15.80.

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² All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

³ Similar results were obtained when the solid was allowed to stand at room temperature for 3 days.