TABLE I

N-SUBSTITUTED *N'*-PHENYLUREAS[a]

$$C_6H_5—NH—\overset{\overset{O}{\|}}{C}—NH—R$$

R	M.P.[b]	Empirical Formula	Calcd. C,%	Calcd. H,%	Calcd. N,%	Found C,%	Found H,%	Found N,%
3-Phenylpropyl-	87- 90	$C_{16}H_{18}N_2O$	75.56	7.13		75.30	7.03	
4-Phenylbutyl-	107–110	$C_{17}H_{20}N_2O$			10.44			10.44
5-Phenylpentyl-	98–100	$C_{18}H_{22}N_2O$	76.56	7.85	9.92	76.11	7.87	10.00
7-Phenylheptyl-	95- 96	$C_{20}H_{26}N_2O$			9.02			8.89
(2-Methyl-2-phenyl)ethyl-	136–137	$C_{16}H_{18}N_2O$	75.56	7.13		75.19	6.75	
2-α-Naphthylethyl-	154–156	$C_{19}H_{18}N_2O$	78.62	6.25		78.20	6.35	
3-Cyclohexylpropyl-	112–113	$C_{16}H_{24}N_2O$	73.80	9.29		73.66	8.90	
6-Cyclohexylhexyl-	117–120	$C_{19}H_{30}N_2O$	75.45	10.00	9.26	74.35	9.83	9.34
2-Pyridylmethyl-	128–130	$C_{13}H_{13}N_3O$	68.70	5.77	18.55	68.55	5.55	18.46
3-Pyridylmethyl-	103–105	$C_{13}H_{13}N_3O$	68.70	5.77		68.55	5.80	
4-Pyridylmethyl-	134–136	$C_{13}H_{13}N_3O$			18.50			18.88
2-Thenyl-	165–168	$C_{12}H_{12}N_2OS$	62.04	5.21	12.06	62.01	5.24	12.11
2-Furfuryl-	118–120	$C_{12}N_{12}N_2O_2$	66.65	5.59	12.96	66.77	5.79	13.04
3-Methoxypropyl-	248–249	$C_{11}H_{16}N_2O_2$			13.45			13.23

[a] The authors are indebted to Mr. B. S. Gorton for technical assistance with some of these syntheses. [b] M.p. are uncorrected.

The various *N*-substituted *N'*-phenylureas were prepared through the usual procedure by condensing the appropriate amine with phenylisocyanate under anhydrous conditions as indicated in the accompanying equation, and were obtained in essentially quantitative yields. Some physical

$$RNH_2 + C_6H_5—N=C=O \longrightarrow C_6H_5NHCONHR$$

properties and analytical data for the previously unreported derivatives which were prepared are summarized in Table I.

Because of the limited solubility of many of these *N*-substituted *N'*-phenylureas in water, most of the biological assays were carried out using a saturated aqueous solution of the compound as the highest concentration tested. The biological systems studied included an attempt to (a) augment the rate of lettuce seed germination,[7] (b) inhibit hydra tentacle regeneration,[8] (c) inhibit the growth of *Escherichia coli*, and (d) augment the growth inhibition of 2,4-diamino-6,7-diphenylpteridine in *Lactobacillus arabinosus*.[9] Under the testing conditions cited in the references, representative members of each of the homologous series of 6-substituted purine derivatives possessed a significant biological response; however, none of the *N*-substituted *N'*-phenylurea analogs were found to be appreciably active in any of these assay systems. Recently, these compounds were also tested for their ability to stimulate growth in carrot tissue, and no significant growth-promoting effects were observed; in contrast, several of the corresponding 6-substituted aminopurines were active in this test system.[10]

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(7) C. G. Skinner, J. R. Claybrook, F. D. Talbert, and W. Shive, *Plant Physiol.*, **32**, 117 (1957.)

(8) C. G. Skinner, W. Shive, R. G. Ham, D. C. Fitzgerald, Jr., and R. E. Eakin, *J. Am. Chem. Soc.*, **78**, 5097 (1956).

(9) E. M. Lansford, Jr., C. G. Skinner, and W. Shive, *Arch. Biochem. Biophys.*, **73**, 191 (1958).

(10) The authors are indebted to Dr. E. M. Shantz, Cornell University, for a preliminary report of these data.

The Mechanism of the *N,N*-Dichloro-*sec*-alkylamine Rearrangement

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In recent papers[1,2] on the rearrangement of *N,N*-dichloro-*sec*-alkylamines to α-amino ketones Baumgarten and coworkers visualize a mechanism similar to that proposed by Cram and Hatch[3,4] for the Neber rearrangement of oxime tosylates. A key intermediate in this reaction sequence is the dehydrohalogenation of the *N,N*-dichloroamine to

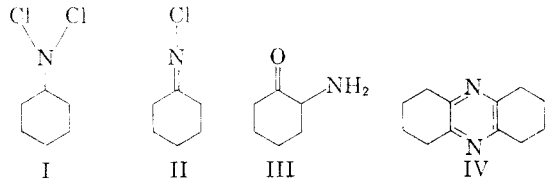
(1) H. E. Baumgarten and F. A. Bower, *J. Am. Chem. Soc.*, **76**, 4561 (1954).

(2) H. E. Baumgarten and J. H. Petersen, *J. Am. Chem. Soc.*, **82**, 459 (1960).

(3) D. J. Cram and M. S. Hatch, *J. Am. Chem. Soc.*, **75**, 33 (1953).

(4) M. S. Hatch and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 38 (1953).

the *N*-chloroimine. The *N*-chloroimine being isoelectronic with the oxime tosylate can then undergo closure to an azirine intermediate, evidence for which has already been presented.[2] Positive evidence that the *N*-chloroimine is an intermediate is now submitted.



I II III IV

Treatment of *N,N*-dichlorocyclohexylamine, I, with potassium acetate in ethanol at the reflux temperature gave *N*-chlorocyclohexylimine, II,[5,6] as a colorless liquid. The compound was characterized by its infrared spectrum, elemental analysis and by its conversion to cyclohexanone on hydrolysis with aqueous acid. Treatment of II with one mole of sodium methoxide in absolute methanol gave an excellent yield of 2-aminocyclohexanone, III, isolated and characterized by its conversion to 1,2,3,4,6,7,8,9-octahydrophenazine, IV.[7]

The conversion of II to III with one mole of base proceeds at least as well as the conversion of I to III with two moles of base, so that the *N*-chloroimine II appears to be an intermediate in the *N,N*-dichloro-*sec*-alkylamine rearrangement.

EXPERIMENTAL

N-Chlorocyclohexylimine. To a solution of 25 g. (0.25 mole) of potassium acetate in 130 ml. of absolute ethanol at the reflux temperature was added dropwise over a period of 30 min. 16.8 g. (0.1 mole) of *N,N*-dichlorocyclohexylamine.[1] The reaction mixture was heated for a further 3 hr., cooled to room temperature and 200 ml. of ether and 100 ml. of benzene added. The ethereal solution was washed with 3 × 100 ml. of water, then with 3 × 50 ml. of 2*N* hydrochloric acid and again with water. The solvent layer was dried with calcium sulfate and the solvent removed at room temperature under vacuum. The residue consisted of 13 g. of an oil which was submitted to vacuum distillation through a column at 3 mm. of mercury. After a small forerun, the product distilled at 53–54°. The product was redistilled to give 7.5 g. (57%) of *N*-chlorocyclohexylimine, b.p. 36°/1.5 mm., n_D^{25} 1.5056. The infrared spectrum showed absorption due to C=N at 1612 cm.$^{-1}$, probably displaced from its normal position because of the chlorine.

Anal. Calcd. for $C_6H_{10}ClN$: C, 54.75; H, 7.66; Cl, 26.94; N, 10.65. Found: C, 54.92; H, 7.82; Cl, 26.68; N, 10.53.

Acid hydrolysis of N-chlorocyclohexylimine. A solution of 0.2 g. of *N*-chlorocyclohexylimine in aqueous ethanol was heated on the steam bath with 1 ml. of concd. hydrochloric acid for 30 min. The reaction mixture was treated with 2,4-dinitrophenylhydrazine reagent and on cooling cyclohexanone 2,4-dinitrophenylhydrazone, m.p. and mixture m.p. 160–162° crystallized.

Rearrangement of N-chlorocyclohexylimine. A solution of 1.0 g. (0.0075 mole) of *N*-chlorocyclohexylimine in 20 ml. of methanol was treated with 8 ml. of a 1.0*N* solution of sodium methoxide in methanol at the reflux for 1 hr. The solution was cooled and 30 ml. of dry ether added. The sodium chloride produced was filtered and amounted to 410 mg. (92%). The ethereal solution was extracted with 3 × 70 ml. of 10% hydrochloric acid and with water. The combined aqueous extracts were heated on the steam bath for 15 min., 30 ml. of 50% sodium hydroxide solution and 5 ml. of 30% hydrogen peroxide were then added, and the heating was continued for a further 15 min. The reaction mixture was cooled in ice and the precipitate filtered. The solid was recrystallized from acetone giving 530 mg. (74%) of 1,2,3,4,6,7,8,9-octahydrophenazine, m.p. 108–109°; mixture melting point with an authentic sample[7] was not depressed.

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(5) S. Reid and D. Sharpe of Central Research Laboratories, Monsanto Chemical Company, Dayton, Ohio (private communication) have also prepared this compound by a different method.

(6) U. S. Patent 2,894,028 claims the preparation of this compound as a crystalline solid, m.p. 20°, by the action of chloramine on cyclohexanone; however, no analysis is given and in our hands the compound failed to crystallize.

(7) P. A. S. Smith, *J. Am. Chem. Soc.*, **70**, 323 (1948).

Three 2-Fluoroalkyl-5-nitrofurans

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In an excellent series of papers[1] sulfur tetrafluoride has recently been introduced as a unique fluorinating agent. By means of this reagent aldehydes and ketones are readily converted to *gem*-difluoro compounds and carboxylic acids to trifluoromethyl derivatives. Using sulfur tetrafluoride we have been able to obtain three 2-fluoroalkyl-5-nitrofurans. This type of nitrofuran has not previously been reported. Thus sulfur tetrafluoride reacted with 5-nitro-2-furaldehyde to form 2-difluoromethyl-5-nitrofuran, with 2-acetyl-5-nitrofuran to give 2-(α,α-difluoroethyl)-5-nitrofuran, and with 5-nitro-2-furoic acid to produce 2-trifluoromethyl-5-nitrofuran.

All of the fluoroalkylnitrofurans had antibacterial activity. The most active member of the group was 2-difluoromethyl-5-nitrofuran. In a two-fold agar dilution test[2] this compound completely inhibited the growth of *Escherichia coli* and *Salmonella typhimurium* at a concentration of 6 mcg. per ml., *Staphylococcus aureus* at 12 mcg. per ml. and *Proteus vulgaris* at 25 mcg. per ml.

(1) W. C. Smith, *et. al.*, *J. Am. Chem. Soc.* **81**, 3165 (1959); C. W. Tullock, *et. al.*, *J. Am. Chem. Soc.*, **82**, 539 (1960); W. R. Hasek, *et. al.*, *J. Am. Chem. Soc.*, **82**, 543 (1960); W. C. Smith, *et. al.*, *J. Am. Chem. Soc.*, **82**, 551 (1960).

(2) Carried out by R. J. Otto and staff of Abbott Laboratories.