refluxed for 12 hr., cooled, and 150 ml. of water was added. The mixture was stirred until both layers became clear, the aqueous layer was separated and extracted with 100 ml. of toluene. The combined toluene solutions were dried over magnesium sulfate, the solvent was removed, and the residue was distilled.

Method E. By the use of a described method,[24] products were obtained from the interaction of benzylidenebenzylamine and ethyl α-bromopropionate (compound 18) or ethyl α-bromoisobutyrate (compound 19); from benzylidenemethylamine and ethyl bromoacetate (compound 12) or ethyl α-bromopropionate (compound 17); from benzylideneaniline and ethyl α-bromophenylacetate (compound 16).

2-Phenyl-3-(benzylamino)propanol. (*a*) 1-Benzyl-3-phenyl-2-azetidinone (1.2 g., 0.005 mole), dissolved in 50 ml. of ether, was added, dropwise, to a stirred suspension of 0.19 g. (0.01 mole) of lithium aluminum hydride in 30 ml. of ether, and the mixture was refluxed for 24 hr. Water (0.5 ml.) was added to the cooled mixture and it was stirred for 4 hr., filtered, the filtrate was dried with magnesium sulfate and the solvent was removed. The residue was recrystallized from ether–petroleum ether (30–40°); m.p. 52–54°[25]; yield 0.9 g. (75%).

Anal. Calcd. for $C_{16}H_{19}ON$: C, 79.64; H, 7.93. Found: C, 79.52; H, 7.79.

The *hydrochloride*, prepared by the use of ethereal hydrogen chloride, melted at 131–133°[26] after recrystallization from 2-butanone.

Anal. Calcd. for $C_{16}H_{20}ONCl$: C, 69.18; H, 7.26; Cl, 12.76. Found: C, 69.23; H, 7.13; Cl, 12.65.

(*b*) Ethyl α-phenyl-β-(benzylamino)propionate (27.4 g.), dissolved in 200 ml. of ether, was added, dropwise, to a stirred suspension of 2.3 g. of lithium aluminum hydride in 300 ml. of ether. The mixture was stirred for 3 days at room temperature; 6 ml. of water was added, dropwise, and the stirring was continued for 24 hr. The mixture was filtered, the filtrate was dried, and the solvent was removed. The oily residue, after it had crystallized, was recrystallized from ether–petroleum ether (30–40°); m.p. and mixed m.p. 52–54°; yield 21.8 g. (94%). The hydrochloride melted at 132–133° after recrystallization from 2-butanone.

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[24] H. Gilman and M. Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).

[25] Ref. 22, m.p. 64°.

[26] Ref. 22, m.p. 135–136°.

[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

Reaction of Alkyl Isocyanides with Ozone. A New Isocyanate Synthesis[1]

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The reactions of alkyl isocyanides with ozone have been shown to give exclusively the corresponding isocyanates. The formation of the isocyanates varied from 7–73%, based upon the conversion of the isocyanates with ammonia to the urea. It appears that increasing concentrations of ozone will result in excellent yields of isocyanates.

The reactions of isocyanides have been studied since their discovery in 1867.[3,4] The only reference in which the oxidation of isocyanides has been investigated dates back to the work of Gautier who found that methyl isocyanide and ethyl isocyanide were oxidized by mercuric oxide[5]; he obtained a complex mixture from which he was able to isolate a small amount of isocyanate.

The purpose of this research was to study the course and the products of the oxidation of isocyanides. Ozone was chosen because it was thought best to employ a very strong oxidizing agent which would also make the separation of products, reactants and starting material fairly easy.

The first isocyanide to be ozonized was isopropyl isocyanide. The materials obtained upon distillation of the reaction mixture were isopropyl isocyanate (identified as the diisopropylurea), unreacted isocyanide, and some residual tars. It became apparent after two preliminary runs that much of the isopropyl isocyanide was being lost through entrainment (*i.e.*, evaporation), and that the separation of the isocyanate from any unreacted isocyanide by distillation was unfeasible because extensive tar formation took place during the distillation.

To avoid these losses, the reaction vessel was provided with a Dry Ice condenser, and the isocyanate was derivatized. It is well known that isocyanates react with amines to give excellent yields of the urea.[6,7] Thus, in all the ozonolysis experiments, the isocyanate was reacted with ammonia and the yield of isocyanate was based upon the amount of urea formed. As a check upon the validity of this method, hexyl isocyanate, prepared by the phosgenation of hexylamine hydrochloride, was reacted with ammonia to give the urea. This was found to proceed in yields of 95–97% in each of four determinations.

The reaction of ethyl, isopropyl, *n*-butyl, *n*-hexyl, and *n*-octyl isocyanides with ozone was studied and the results are shown in Table I.

From the data in the table it may be noted that

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[1] Abstracted in part from the Ph.D. thesis of Harry Rubinstein, (February 1958).

[2] Purdue Research Foundation Fellow, 1956–58.

[3] A. W. Hofman, *Compt. rend.*, **65**, 484 (1867).

[4] A. Gautier, *Ann. Chim.* (*Paris*) (4), **17**, 228 (1869).

[5] A. Gautier, *Ann.*, **149**, 313 (1869).

[6] W. Siefken, *Ann.*, **562**, 99 (1949).

[7] Houben-Weyl, *Methoden Der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, Germany (1952) Volume 8, p. 157.

TABLE I

REACTION OF VARIOUS ISOCYANIDES WITH OZONE

Isocyanide	B.P., °C.	Mole	Reaction Time, Hr.	Vol. of O_2, L.	Approx. Amt. of O_3 Produced, Mole	Isocyanate,[a] % Conversion	Isocyanide Lost by Entrainment, Moles × 10^{-3}	Isocyanide Unreacted, Moles × 10^{-3}	Isocyanate, % Yield
Ethyl[b]	77	0.105	10	84.0	0.10	7.1	4.84	91	83
Isopropyl[c,d]	85–87	0.143	14	174.5	0.14	34	—	—	—
n-Butyl[c]	123–124.5	0.127	13	152.7	0.13	37	—	—	—
n-Hexyl[c]	168–169	0.121	15	199.0	0.15	55	5.05	40	88
n-Octyl[c]	89–91/12 mm.	0.081	25	272	0.25	73.5	5.90	3.2	82

[a] Based on the formation of the urea. [b] Reaction temperature 0°. [c] Reaction temperature 25°. [d] In ethylene chloride as solvent.

the higher molecular weight isocyanides gave conversions to the isocyanates than the lower ones. This seems to be due primarily to the volatility of the isocyanides and isocyanates involved. For example, when ethyl isocyanide was ozonized at 25°, the loss through entrainment (despite the use of the Dry Ice condenser and a Dry Ice trap), was so large that the reaction had to be carried out at 0°. Even then the loss was appreciable and the flow of oxygen and the reaction time had to be decreased. These factors and the lower reaction temperature, account for the low conversion in the case of ethyl isocyanide.

In order to establish that isocyanates were the only products in the ozonolysis of isocyanides, the ozonolysis mixture of octyl isocyanide was reacted with ammonia. The filtrate from this reaction mixture gave on distillation only unreacted isocyanide, without significant tar formation. When, however, the crude ozonolysis product was distilled, tar formation took place. This very likely was caused by decomposition or polymerization of the isocyanate present.

It is apparent, therefore, that the reactions of isocyanides with ozone are potentially capable of giving excellent yields of isocyanates. In order to achieve this, it would be necessary to produce higher concentrations of ozone, thereby decreasing the over-all reaction time. This is especially desirable in the case of the lower boiling isocyanides.

EXPERIMENTAL

Preparation of isocyanides. Ethyl isocyanide. Ethyl isocyanide was prepared according to the procedure of H. L. Jackson and B. C. McKusick[8] in 75% yields, b.p. 77° (lit. val., 78°).

All other isocyanides were prepared by minor modification of a published procedure.[9]

Isopropyl isocyanide. Isopropyl isocyanide was prepared in a yield of 71%, b.p. 85–87° (lit. val., 87°).[10]

n-Butyl isocyanide. In the preparation of *n*-butyl isocyanide the reaction mixture was heated to 120–140° for 2 hr. and the oil layer formed was separated by decanting it from the frozen water layer. Yield 84%, b.p. 123–124.5° (lit. val.,[11] 124–125°).

n-Hexyl isocyanide. In the synthesis of *n*-hexyl isocyanide the reaction mixture was heated at 115–120° for only 1 hr. and after distillation a 63% yield was obtained, b.p. 168–169°.

Anal. Calcd. for $C_7H_{13}N$: C, 75.6; H, 11.7; N, 12.6. Found: C, 75.32; H, 12.00; N, 12.50.

n-Octyl isocyanide. This compound was prepared in exactly the same manner as the hexyl isocyanide affording an 89% yield of liquid, b.p. 89–91°/12 mm.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.2; N, 10.05. Found: C, 77.48; H, 12.45; N, 10.06.

Octyl isocyanate. Except for variations in reaction time and amount of ozone produced (*cf.* Table I) this preparation is typical of the procedure employed.

The ozonizer used was that proposed by Henne and Perilstein,[12] except that the reaction cell was provided with a Dry Ice condenser.

n-Octyl isocyanide (11.3 g., 0.08 moles) was placed into the reaction cell and treated with ozonized oxygen at 25°. This was done on two successive days using 272 l. of oxygen (approx. 0.25 mole of ozone) in 25 hr. The reaction cell was stored in Dry Ice between the runs. At the end of 25 hr. the system was flushed with oxygen and the product weighed. A total of 9.15 g. of liquid was obtained and this was treated with excess ammonia gas at Dry Ice temperature. The

TABLE II

UREA DERIVATIVES PREPARED FROM ISOCYANATES

Urea	Recrystallized	M.P., °C.
Isopropyl[13,a]	Ethyl acetate	154
n-Butyl[14]	Benzene	96
n-Hexyl[15]	Benzene	108–110
n-Octyl	Benzene	100–101

[a] Was prepared by the addition of concentrated ammonium hydroxide to the ozonolysis reaction mixture.

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(8) *Org. Syntheses*, **35**, 62 (1955).

(9) Reference (**7**), p. 135.

(10) A. Gautier, *Ann.*, **149**, 155 (1869).

(11) T. L. Davis, *J. Am. Chem. Soc.*, **59**, 1998 (1937).

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(13) C. H. Maugin, *Ann. de Chemie*, *8E*, **22**, 321 (1911).

(14) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, **51**, 1797 (1929).

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excess ammonia was then allowed to escape, with intermittent stirring, and the resulting solid was filtered and dried *in vacuo* for 24 hr. This procedure gave 8.25 g. (60%) of a slightly brown material which was recrystallized three times from benzene to give *n*-octylurea, m.p. 100–101°.

Anal. Calcd. for $C_9H_{20}N_2O$: C, 62.70; H, 11.62; N, 16.27. Found: C, 62.47; H, 11.62; N, 16.29.

The ureas which were prepared from the isocyanates, resulting from the ozonolysis of the various isocyanides are listed in Table II.

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LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

Action of Base on Certain Pyridinium Salts[1,2]

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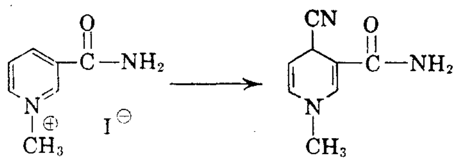
The action of ethoxide, hydroxide, and cyanide ions on a number of 1-alkyl-3-substituted pyridinium salts has been studied and interpreted. Evidence for the formation of pseudo bases and, in one case, the dimolecular ether of a hydroxy pseudo base has been obtained.

Among the properties of di- and triphosphopyridine nucleotides (DPN and TPN) which have been attributed to the nicotinamide portion of the molecule is the reaction with nucleophilic species to give a change in the ultraviolet absorption similar to that observed on reduction to the dihydro compounds. This behavior was first noted with cyanide and bisulfite by Meyerhof *et al.*[3] More recently the reaction with cyanide has been studied in some detail with the coenzymes and also with model compounds including a number of 3-substituted 1-methylpyridinium iodides.[4] From deuterium exchange experiments San Pietro[5] concluded that the reaction involved the addition of cyanide to the 4-position of DPN to form a pseudo cyanide. Recently a stable, crystalline cyanide addition product (II) has been isolated from I.[6] Also the spectral changes observed with the model compounds[4] seem to correspond best to 4-cyano derivatives. Other reactions which probably involve addition of a nucleophilic group at the 4-position are those with acetone,[7] negatively substituted methyl ketones,[8] and hydroxylamine.[9]


I II

The transient existence of pseudo bases has long been suspected in the formation of pyridones from *N*-alkylpyridinium halides[10] and in the reaction of strong alkali with DPN,[11] but there is very little evidence in support of this hypothesis.[10,12]

In connection with the preparation of a number of 1-alkyl-3-substituted-1,4-dihydropyridines as model compounds of DPNH,[13] it was observed that the aqueous solution of the quaternary pyridinium halide and sodium carbonate became yellow before the introduction of the sodium dithionite. In the case of one compound, 1-benzyl-3-acetylpyridinium chloride, a yellow solid also precipitated. Accordingly, the effect of base on the absorption spectra of ethanolic solutions of the substituted pyridinium halides was qualitatively measured and it was found that a similar spectral change occurred for all of the model compounds (Table I). Each of these had a substituent attached *via* a carbonyl group to the 3-position. The spectrum of a compound having no such group, 1-benzylpyridinium chloride, was essentially the same in neutral, basic, and acidic solutions.

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[1] From the Ph.D. thesis of Gerald Berkelhammer.

[2] Supported in part by a research grant (No. RG-3844) from the National Institutes of Health, Public Health Service.

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