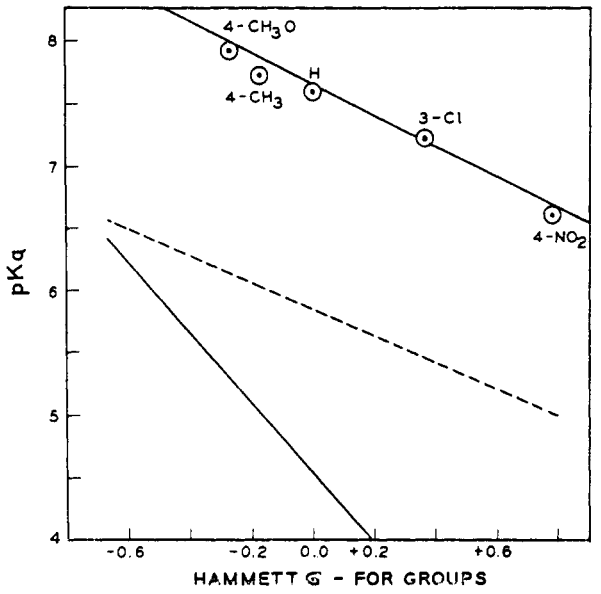

Fig. 1 Correlation of pK_a values with Hammett sigma values of groups ⊙——⊙ 4-phenyl-5-(substituted phenyl) amino-1,2,3-triazoles. - - - - - - - 5-(substituted phenyl) aminotetrazoles. ——Mono-substituted anilines

IV, is similar to that of the tetrazoles. From the previous study by Lieber, Rao, and Chao,[13] it has been concluded that it is the heterocyclic proton rather than the proton on the exo-nitrogen atom that is the source of the acidity of types IV and VI compounds. The correspondence of the rho-values in these two systems is therefore easily understood.

Both IV and VI undergo thermal isomerizations which involve an equilibrium.[1,2,14] A plot of the pK_a values of IV *vs.* the equilibrium constants for IV ⇌ VII at 458°K. in purified ethylene glycol as solvent is essentially linear and similar to the tetrazole system.[10] Generally, as the electronegativity of the substituent increases, the pK_a of IV decreases (Fig. 1) and the position of equilibrium shifts favoring the formation of IV. These results are similar to those obtained for the equilibrium VI ⇌ VIII by Henry, Finnegan, and Lieber.[1] Accordingly, these data confirms the common electronic mechanism suggested[14] for these two equilibria.

Acknowledgment. The authors gratefully acknowledge the support of the Research Corp. which made these studies possible.

CHICAGO, ILL.

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(14) E. Lieber, C. N. R. Rao, and T. S. Chao, *J. Am. Chem. Soc.*, **79**, 5962 (1957).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

Nitriles in Nuclear Heterocyclic Synthesis. II

ALBERT I. MEYERS[1] WITH JOHN J. RITTER

Received May 19, 1958

Reaction of 2,5-dimethyl-2,5-hexanediol, 2,4-dimethyl-2,4-pentanediol, and methallyl mercaptan with nitriles in concentrated sulfuric acid yields Δ^1-pyrrolines, dihydropyridines, and 2-thiazolines, respectively. This new heterocyclic ring-closure has been accomplished with a variety of nitriles.

Previously reported nuclear syntheses of nitrogen heterocycles from nitriles have been limited in number. Dilthey[2] and Janz[3] have succeeded in condensing nitriles with dienes at elevated temperatures. The formation of a dihydroisoquinoline from methyleugenol and veratronitrile was reported by Ritter and Murphy.[4] Quilico[5] and

(1) Abstracted from the dissertation submitted by Albert I. Meyers to the Graduate Faculty of New York University in partial fulfillment of the requirements for the Ph.D. degree.

(2) M. Dilthey, *Ber.*, **68**, 1162 (1935).

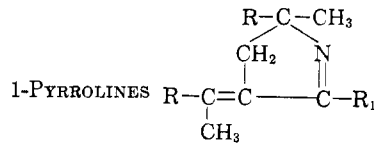
(3) G. J. Janz, W. McCulloch, and S. C. Wait, Jr., *J. Am. Chem. Soc.*, **77**, 3014 (1955); G. J. Janz and M. A. DeCrescente, *J. Org. Chem.*, **23**, 765 (1958).

(4) J. J. Ritter and F. X. Murphy, *J. Am. Chem. Soc.*, **74**, 763 (1952).

(5) A. Quilico, G. Stango d'Alcontres, and P. Grunanger, *Nature*, **166**, 226 (1950).

TABLE I

1-PYRROLINES



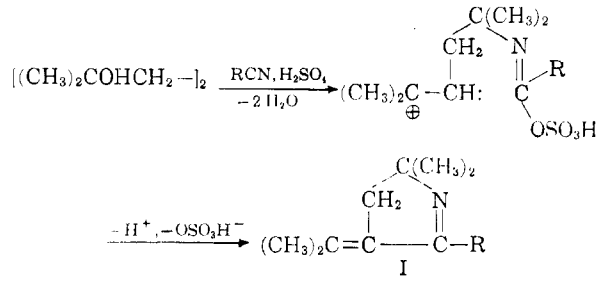
No.	R	R_1	B.P., °C./ Mm. Hg	n'_D	d_{25}^{25a}	Yield, %	Formula	N Calcd.	N Found	Picrate M.P.,[b] °C.
1	CH_3	CH_3	78–79/14	1.4840[25]	0.872	80	$C_{10}H_{17}N$[c]	9.2	9.2	186–187
2	CH_3	CH_2=CH	60–62/5	1.5031[19]	0.901	78[d]	$C_{11}H_{17}N$	8.6	8.7	110[e] (dec.)
3	CH_3	C_6H_5	120–122/5	1.5480[18]	0.979	72	$C_{15}H_{19}N$	6.6	6.5	160–161
4	CH_3	p-$NO_2C_6H_4$	140–143/2[e]	—	—	78	$C_{15}H_{18}N_2O_2$	10.7	10.5	172–173
5	CH_3	p-$CH_3OC_6H_4$	138/140/2	1.5540[25]	1.029	71	$C_{16}H_{21}ON$	5.7	5.7	159–160
6	CH_3	3-C_5H_4N	105–107/2	1.5490[17]	1.021	62	$C_{14}H_{18}N_2$	130.	12.8	140–141
7	CH_3	4-C_5H_4N	110–112/1[f]	—	—	55	$C_{14}H_{18}N_2$	13.0	12.8	192–193
8	C_2H_5	CH_3	73–75/3	1.4720[25]	0.977	56	$C_{12}H_{21}N$[h]	7.8	7.4	[g]

[a] A 1-cc. pycnometer calibrated against water at 25° was used. [b] Analyses were all in good agreement with calculated values. [c] Calcd.: C, 79.6; H, 11.2. Found: C, 79.5; H, 11.2. [d] Crude product. Successive distillations caused about 30% loss through thermal polymerization. [e] M.p. 71–72°. [f] M.p. 69–70°. [g] No picrate formed. [h] Calcd.: C, 80.4; H, 11.7. Found: C, 80.1; H, 11.5.

Marxer[6] prepared heterocycles containing two heteroatoms from nitriles and their derivatives. In a previous communication[7] one of us reported the reaction of 2-methyl-2,4-pentanediol with nitriles to form dihydroöxazines. This novel ring-closure has now been extended to the synthesis of 5,5-dimethyl-3-isopropylidene-1-pyrrolines, 4,6,6-trimethyl-5,6-dihydropyridines, and 4,4-dimethyl-2-thiazolines.

1-Pyrrolines. Treatment of 2,5-dimethyl-2,5-hexanediol with acetonitrile in concentrated sulfuric acid produced 2,5,5-trimethyl-3-isopropylidene-1-pyrroline (1) in 80% yield. 2,5-Dimethyl-2,4-hexadiene under the same conditions gave a much smaller yield (28%) of the product (I) along with much polymeric material. A series of 1-pyrrolines was obtained in yields of 50–80% from other nitriles (Table I), using the diol throughout rather than the related diene.

This reaction can be regarded as an extension of the *N*-alkylamide synthesis[8] and may be formulated as follows:



It would appear that the presence of a nucleophilic center suitably placed in the primary adduct may alter the final step and lead to a heterocyclic base instead of the usual amidic product.

The structure of I was confirmed by isolation of acetone as a product of permanganate oxidation and formation of a tetrahydro derivative. Intense infrared bands were observed at 1587 cm.$^{-1}$ and 1640 cm.$^{-1}$, consistent with the values reported for the cyclic conjugated C=N and C=C links[9] (Fig. 1). Determination of the exact spectral positions of the C=N and C=C links for this type of compound was made by examining the spectra of its dihydro (Fig. 2) and tetrahydro (Fig. 3) derivatives. Fig. 2 shows only one band (1650 cm.$^{-1}$) while Fig. 3 shows no significant absorption in the 1500–2600 cm.$^{-1}$ region. Apparently

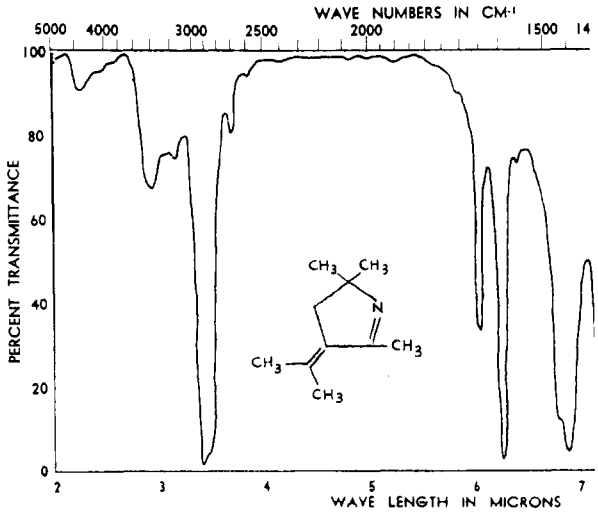


Figure 1

(6) A. Marxer, *Helv. Chim. Acta*, **37**, 166 (1954); *J. Am. Chem. Soc.*, **79**, 467 (1957).

(7) J. J. Ritter and E. J. Tillmanns, *J. Org. Chem.*, **22**, 839 (1957).

(8) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4048 (1948).

(9) H. M. Randell, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, Van Nostrand, N. Y., 1949, p. 211; G. W. Perold, A. P. Steyn, and F. V. K. von Reiche, *J. Am. Chem. Soc.*, **79**, 462 (1957).

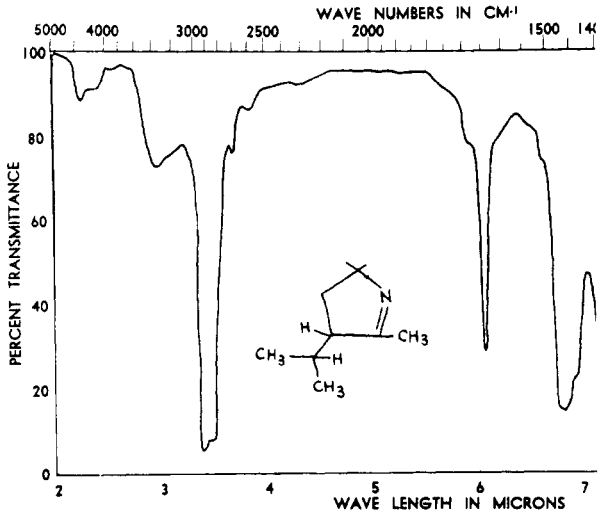


Figure 2

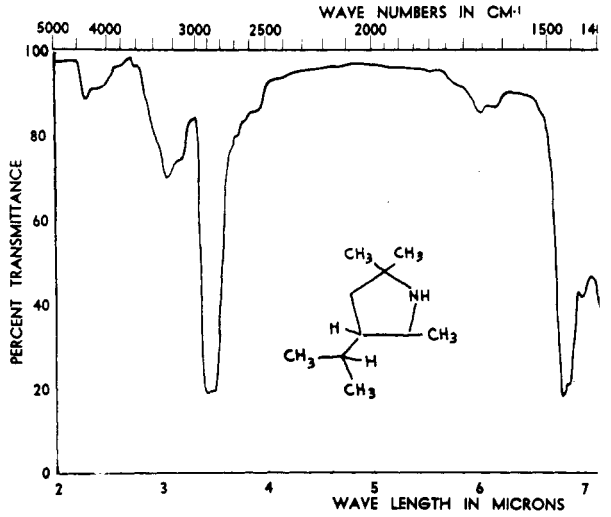
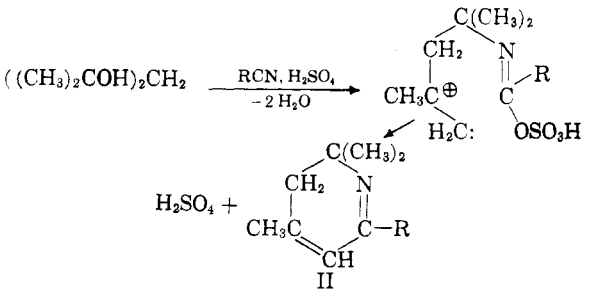


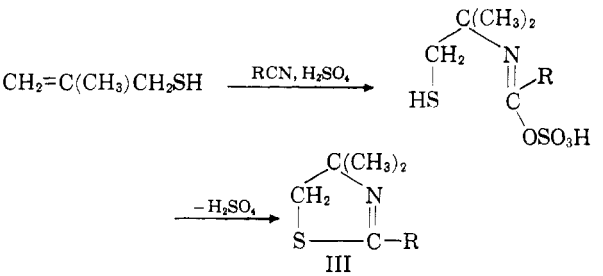
Figure 3

loss of the conjugation by hydrogenation of the C=C link has eliminated the 1640 cm.$^{-1}$ band and shifted the 1587 cm.$^{-1}$ band to shorter wave lengths. The medium band at 1650 cm.$^{-1}$ is in good agreement with that reported[10] for the cyclic unconjugated C=N link in 1-pyrrolines. All of the pyrrolines prepared in this work showed strong absorption in the 1565–1612 cm.$^{-1}$ region, which may be attributed to the conjugated cyclic C=N link.

5,6-Dihydropyridines. Reaction of 2,4-dimethyl-2,4-pentanediol with acetonitrile in concentrated sulfuric acid formed 2,4,6,6-tetramethyl-5,6-dihydropyridine (II). Benzonitrile and acrylonitrile yielded the 2-phenyl and 2-vinyl analogs of II (Table II). The low yields of heterocyclic base from 2,4-dimethyl-2,4-pentanediol are caused mainly by its cleavage to acetone and isobutene in sulfuric acid.[11] Isobutene reacts with the nitrile to yield an *N-tert*-butyl-amide.[8] In the case of acetonitrile this product was isolated in 50–55% yield. Compound II was identified by aromatization to 2,4,6-collidine followed by oxidation to isonicotinic acid.



2-Thiazolines. 2-Thiazolines (III) were formed in about 25% yields when methallyl mercaptan was treated with nitriles in sulfuric acid. The identity



of 2,4,4-trimethyl-2-thiazoline (III, R = CH_3) was confirmed by its preparation from *N*-(2-chloro-*tert*-butyl)-acetamide by treatment with phosphorus pentasulfide.[12] Infrared spectra of the thiazolines prepared in this study showed only one strong band in the 1500–1700 cm.$^{-1}$ region, lying between 1587 and 1641 cm.$^{-1}$

EXPERIMENTAL

Materials. 2,5-Dimethyl-2,5-hexanediol (m.p. 88–89°) was obtained from the Air Reduction Chemical Co. and was used without further purification. Methallyl mercaptan (b.p. 92-93°) was provided by the Fairfield Division of Food Machinery and Chemical Corp. and was used as received. 2,4-Dimethyl-2,4-pentanediol (b.p. 98–100°/14 mm.) was prepared by condensation of diacetone alcohol with methylmagnesium bromide.[13] Spectra were measured on the Baird Recording Spectrophotometer Model BA-2. All melting and boiling points are corrected.

General procedure. Concentrated sulfuric acid (200 g.) in a 500-ml. three-necked flask fitted with a dropping funnel, thermometer, and mechanical stirrer was cooled to 3° in

(10) G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951); L. J. Bellamy, *The Infrared Absorption of Complex Molecules*, Methuen and Co. Ltd., London 1954, p. 227.

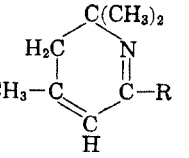
(11) H. E. Zimmerman and J. English, Jr., *J. Am. Chem. Soc.*, **76**, 2285 (1954); F. V. Brutcher and J. English, Jr., *J. Am. Chem. Soc.*, **74**, 4279 (1952).

(12) S. H. Babcock and R. Adams, *J. Am. Chem. Soc.*, **59**, 2260 (1937). R. Lusskin and J. J. Ritter, *J. Am. Chem. Soc.*, **72**, 5577 (1950) reported the melting point of *N*-(2-chloro-*tert*-butyl)acetamide as 200°. This is actually the melting point of the isomeric oxazoline hydrochloride, formed by spontaneous rearrangement of the amide at room temperature. The amide, recrystallized from 35–60° petroleum ether immediately after isolation, melts at 68–69°.

(13) A. Frank and M. Kohn, *Monatsh.*, **28**, 997 (1908).

TABLE II

5,6-DIHYDROPYRIDINES

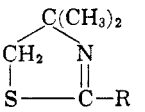


No.	R	B.P., °C./ Mm. Hg	n^t_D	d^{25}_{25}	Yield, %	Formula	N Calcd.	N Found	Picrate M.P.,[a] °C.
1	CH_3	60–62/16	1.4425^{20}	0.959	23	$C_9H_{15}N$[b]	10.2	10.4	173–175
2	CH_2=CH	73–74/18	1.4725^{25}	0.947	20	$C_{10}H_{15}N$	9.3	9.2	141–143
3	C_6H_5	116–118/4	1.5361^{21}	1.003	21	$C_{14}H_{16}N$	7.0	6.9	167–168 (dec.)

[a] Analyses were all in good agreement with calculated values. [b] Calcd.: C, 78.8; H, 10.9. Found: C, 78.5; H, 10.6.

TABLE III

4,4-DIMETHYL-2-THIAZOLINES



No.	R	B.P., °C./ Mm. Hg	n^{25}_D	d^{25}_{25}	Yield, %	Formula	N Calcd.	N Found	Picrate M.P.,[a] °C.
1	CH_3	146–148/atm.	1.4825	0.969	25	$C_6H_{11}NS$[b]	10.8	10.8	171–172
2	CH_2=CH	55–57/6	1.5040	0.998	23	$C_7H_{11}NS$	9.9	8.7[d]	[c]
3	C_6H_5	137–138/9	1.5572	1.030	24	$C_{11}H_{13}NS$	7.4	7.3	142–143

[a] Analyses were all in good agreement with calculated values. [b] Calcd.: C, 55.9; H, 8.5. Found: C, 56.2; H, 8.8. [c] Treatment with picric acid gave polymeric material. [d] Incomplete combustion noted during analysis. Infrared absorption agrees well with 2-thiazoline values.

TABLE IV

INFRARED BANDS OF 1-PYRROLINES AND 2-THIAZOLINES IN THE 1500–1700 CM.$^{-1}$ REGION[a]

No.	1-Pyrrolines (Table I) Cm.$^{-1}$	2-Thiazolines (Table III) Cm.$^{-1}$
1	1587s, 1640m	1641s
2	1575s, 1640m	1587s
3	1562s, 1645m	1615s
4	1570s, 1645m	
5	1612s, 1643m	
6	1572s, 1642m	
7	1572s, 1649m	

[a] s, strong; m, medium.

an ice bath. The nitrile (0.25 mole) was added dropwise (or portionwise if solid) during 15 min. at 5–7°. The glycol was then added during 2 hr. at 9–12°. The resulting pale yellow solution was stirred 2 hr. more with ice cooling, then poured on 300 g. of cracked ice. After 2 hr. standing the brown aqueous mixture was extracted with chloroform to remove polymeric and other non-basic by-products. The aqueous layer was separated, cooled to 5°, and made strongly alkaline with 35% sodium hydroxide solution. The product appeared as a supernatant oil which was separated, and the aqueous layer was extracted with ether and the extracts combined with the separated product. After drying over anhydrous potassium carbonate in a nitrogen atmosphere the ether was removed and the product was distilled *in vacuo*. All pyrrolines and dihydropyridines were prepared in this manner. In the preparation of thiazolines the only departure from the above was the use of two moles of nitrile to one of mercaptan. The dihydropyridines were accompanied by large amounts of *N-tert*-butylamide. In the experiment where acetonitrile was used this was isolated from the ethereal extracts, which contained both heterocyclic base and amide, but extraction with 5% aqueous hydrochloric acid to remove the dihydropyridine. The remaining ether solution was then extracted with concentrated hydrochloric acid to remove the amide, which was recovered from the acid layer by dilution and neutralization with 20% sodium hydroxide solution. It separated as an oil which solidified on standing and was recrystallized from petroleum ether.

Oxidation of I. A suspension of I (5 ml.) in 100 ml. of water was cooled to 0° and a previously cooled solution of potassium permanganate (18 g.) in 200 ml. of water was added dropwise with vigorous stirring at 0–5°. Hydrogen peroxide was then added to destroy excess permanganate and the manganese dioxide was removed by filtration. The colorless filtrate was distilled to remove 20 ml. of aqueous distillate containing acetone which was isolated as its dinitrophenylhydrazone, m.p. 126–128° alone and in mixed melt with an authentic specimen.

Aromatization of II. The dihydropyridine II (5 ml.) was dissolved in 10 ml. of isoamyl disulfide and the mixture was heated in a flask fitted with a column to take off overhead isoamyl mercaptan (4 ml.) at 115–125°. The dark colored still residue was poured into 25 ml. of 10% hydrochloric acid, the mixture was extracted with benzene to remove excess disulfide, and the aqueous layer was made alkaline. The product, 2,4,6-collidine, appeared as an oil which was extracted with ether and distilled at 60–68°/17 mm. after drying over potassium carbonate and removal of the ether. *Picrate*, m.p. 149–154°; reported,[14] 155°.

Oxidation of 2,4,6-collidine. A mixture of the collidine (4 ml.) and 5% potassium permanganate solution (100 ml.) was heated on the steam bath for 4 hr. The precipitated manganese dioxide was filtered, suspended in 100 ml. of

(14) A. Pictet, *Compt. rend.*, **162**, 876 (1916).

water, and the suspension heated on the steam bath for 1 hr., then filtered. The filtrate was evaporated to small volume and acidified to precipitate impure nicotinic acid. This was washed successively with boiling water and boiling ethanol and air-dried. It yielded an amide, m.p. 155–156° which showed no depression in mixed melt with an authentic specimen.[15]

Hydrogenation of I. (*a*) Dihydroderivative. A solution of I (17.1 g., 0.13 mole) in 50 ml. of anhydrous methanol was hydrogenated at 22° and 30 p.s.i. in presence of 50 mg. of Adams catalyst,[16] and absorbed 0.13 mole of hydrogen in 0.5 hr. The mixture was filtered, the methanol was removed and the product distilled, b.p. 65–66°/12 mm.; n_D^{22} 1.4532; picrate, m.p. 160–161°. (*b*) Tetrahydroderivative. A solution of I (6.5 g., 0.043 mole) in glacial acetic acid (100 ml.) absorbed 0.086 mole of hydrogen at 23° and 40 p.s.i., in presence of 45 mg. of Adams catalyst. The mixture was filtered, diluted with 200 ml. of water, neutralized, and saturated with potassium hydroxide. Ether extraction followed by drying, removal of ether, and distillation yielded the product (5.8 g.) as a colorless oil with irritating odor, b.p. 58–59°/9 mm.; n_D^{22}, 1.4392; phenylthiourea, m.p. 108–109°.

(15) E. Spath and H. Spitzer, *Ber.*, **59**, 1484 (1926).

(16) Roger Adams, V. Voorhees, and R. L. Shriner, *Org. Syntheses*, Coll. Vol. I, 466 (1943).

NEW YORK 3, N. Y.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, JEFFERSON CHEMICAL CO., INC.]

Preparation of Substituted 2-Oxazolidones from 1,2-Epoxides and Isocyanates

GEORGE P. SPERANZA AND W. J. PEPPEL

Received June 30, 1958

Quaternary ammonium halides have been found to be efficient catalysts for the addition of isocyanates to 1,2-epoxides. Substituted 2-oxazolidones are obtained in good yields.

Many basic substances, including tertiary amines, are known to catalyze the polymerization of isocyanates to cyclic dimers or to isocyanurates.[1,2] In reported attempts to prepare substituted 2-oxazolidones from 1,2-epoxides and isocyanates using basic catalysts, only polymerization of the isocyanate has been observed.[3,4]

We have found that quaternary ammonium halides are highly efficient catalysts for the addition of isocyanates to 1,2-epoxides, and substituted 2-oxazolidones are obtained in good yields. An inorganic halide, potassium iodide, selected for its solubility in the reaction mixture, was also found to be a good catalyst. The ability of quaternary ammonium halides to catalyze opening of the oxirane ring has been disclosed in connection with the preparation of alkylene carbonates from alkylene oxides and carbon dioxide.[5]

When ethylene oxide and phenyl isocyanate were heated with a small amount of tetraethylammonium bromide in an autoclave at 200° for one hour, 3-phenyl-2-oxazolidone was obtained in 92% yield. When triethylamine was substituted as the catalyst, triphenyl isocyanurate was observed to be the principal product and 3-phenyl-2-oxazolidone was isolated with difficulty in small amount. Since Jones and Savill found that phenyl isocyanate alone slowly polymerized at room temperature in the presence of cetyl pyridinium chloride, neither type of catalyst is entirely specific.[4]

The preparation of a variety of substituted 2-oxazolidones is summarized in Table I. The reactions with ethylene and propylene oxides were carried out in a rocking autoclave under the autogenous pressure. No attempts were made to determine optimum reaction conditions or to select a preferred inert solvent, several being used mainly to facilitate recovery of the products. Vinylcyclohexene diepoxide and a commercial epoxy resin were used along with 2,4-toluenediisocyanate to obtain polymeric products which were found to have no well defined softening or melting points but otherwise were not characterized further.

The product isolated in 64% yield from the reaction of the unsymmetrical propylene oxide with phenyl isocyanate was shown to be 3-phenyl-5-methyl-2-oxazolidone (I) by comparison with a sample prepared by the method of Homeyer.[6] The intermediate, *N*-2-hydroxypropylaniline, was prepared from aniline and propylene oxide and is known to have the structure shown.[7] Identity of the oxazolidones was confirmed by a mixed melting point determination and the similarity of the infrared spectra.

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(5) M. Lichtenwalter and J. F. Cooper, to Jefferson Chemical Co., Inc., U. S. Patent **2,773,070**, Dec. 4, 1956.

(6) A. H. Homeyer, to Mallinkrodt Chemical Co., U. S. Patent **2,399,118**, Apr. 23, 1946.

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