Reactions of Acetylenic Amines. VIII. Cyclization of Acetylenic Ureas

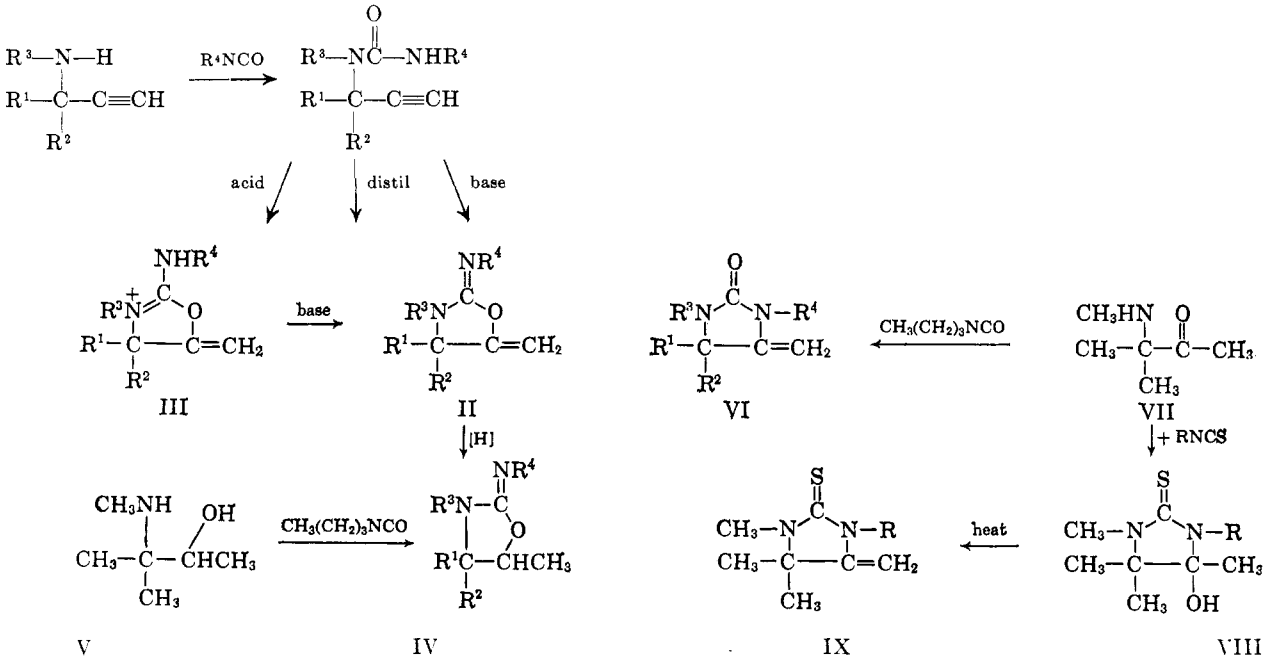
NELSON R. EASTON, DONALD R. CASSADY, AND ROBERT D. DILLARD

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis 6, Indiana

Received January 15, 1964

The cyclizations of ureas prepared from α,α-disubstituted propargylamines gave two isomeric heterocyclic products. Under the influence of heat or strong acid the ureas cyclized to 2-iminooxazolidines. However, base catalyzed the cyclization to imidazolidinones, which were also prepared from the reaction of isocyanates with the appropriate amino ketones. The thioureas from the reaction of the secondary α,α-disubstituted propargylamines with isothiocyanates could not be isolated since they rapidly cyclized to the 2-iminothiazolidines. The thioureas from the primary amines could be isolated but on standing also underwent S-cyclization. However, base-catalyzed cyclization of the freshly prepared thioureas gave the imidazolidinethiones.

The cyclizations of urethanes from tertiary acetylenic carbinols have been reported[1-3] recently. It has been noted[4] also that certain ureas derived from propargylamines cyclize in the presence of phosphorus pentachloride to give imidazolines. Papers[5a,b] have appeared describing the preparation of thiazoles and imidazoles from the reaction of urea or thiourea with halo acetylenes.



a, $R^1 = R^2 = R^3 = CH_3$; $R^4 = CH_3(CH_2)_3$—
b, $R^1 = R^2 = R^3 = R^4 = CH_3$
c, $R^1 = CH_3$; $R^2 = (CH_3)_2CH$—; $R^3 = R^4 = C_2H_5$
d, $R^1 = R^2 = C_2H_5$; $R^3 = CH_3$; $R^4 = CH_3(CH_2)_3$

More recently[6a,b] the same author has shown that 1-(1-methyl-2-propynyl)urea is stable to heat but on treatment with sulfuric acid cyclizes to 4,5-dimethyl-2-imidazolone, presumably through the intermediate, 4-methylene-5-methyl-2-imidazolidinone. We present our findings in this area.

The preparation of the urea Ia was accomplished by the slow addition of *n*-butyl isocyanate to an ethereal solution of N-3,3-trimethyl-1-propynylamine. However, distillation of this material produced a new compound. Since the infrared spectrum of the latter material did not show absorption in the acetylenic CH region, it was assumed that cyclization had taken place. The two most probable structures were those of the methyleneoxazolidine (II) or the methyleneimidazolidinone (VI). The n.m.r. spectrum showed doublets, centered at τ 5.44 and 5.86, which were not present in the starting urea Ia. There were available in these laboratories two excellent models for comparison with this n.m.r. spectrum: 2,3,4,4-tetramethyl-5-methylene-2-oxazolinium chloride (X), which has the $H_2C{=}\overset{|}{C}{-}O{-}$ structure[7]; 5,5-dimethyl-3-ethyl-4-methylene-2-oxazolidinone (XI), which has the $H_2C{=}\overset{|}{C}{-}N{-}$ grouping.[3] The n.m.r. spectrum of X shows two doublets centered at τ 4.93 and 5.35, whereas the n.m.r. spectrum of XI showed doublets centered at τ 5.97 and 6.08.

Although the chemical shifts for the doublets in this new compound are midway between the two models, the difference in chemical shifts between the doublets

(1) S. L. Shapiro, V. Bondurco, and L. Freedman, *J. Org. Chem.*, **26**, 3710 (1961).

(2) K. Sisido, K. Hukuoka, M. Tuda, and H. Nozaki, *ibid.*, **27**, 2663 (1962).

(3) N. R. Easton, Donald R. Cassady, and Robert D. Dillard, *ibid.*, **27**, 2927 (1962).

(4) P. J. Stoffel and A. J. Speziale, *J. Am. Chem. Soc.*, **84**, 501 (1962).

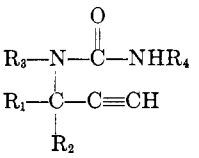
(5) (a) Y. Yura, *Chem. Pharm. Bull. Japan*, **10**, 372 (1962); (b) **10**, 376 (1962); (c) W. Batty and B. Weedon, *J. Chem. Soc.*, 786 (1949).

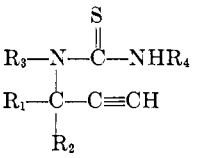
(6) (a) Y. Yura, *Chem. Pharm. Bull. Japan*, **10**, 1087 (1962); (b) **10**, 1094 (1962).

(7) N. R. Easton and R. D. Dillard, *J. Org. Chem.*, **28**, 2465 (1963).

TABLE IA

UREAS AND THIOUREAS



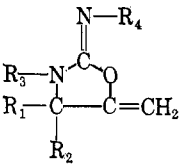


						Analyses, %					
						Calcd.			Found		
R_1	R_2	R_3	R_4	M.p., °C.	Formula	C	H	N	C	H	N
CH_3	CH_3	CH_3	C_2H_5	Liquid	$C_9H_{26}N_2O$	64.25	9.59	16.65	63.97	9.83	16.57
CH_3	CH_3	CH_3	n-$C_{18}H_{37}$	56–57[a]	$C_{25}H_{48}N_2O$	76.47	12.32	7.13	76.31	12.16	7.01
CH_3	CH_3	CH_3	C_6H_5	84–86[b]	$C_{13}H_{16}N_2O$	72.19	7.46		72.28	7.36	
CH_3	CH_3	CH_3	4-ClC_6H_4	87–88[b]	$C_{13}H_{15}ClN_2O$	62.27	6.03	11.17	62.12	6.30	10.93
C_2H_5	C_2H_5	CH_3	n-C_4H_9	Liquid	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.55	10.87	12.65
C_6H_5	H	C_2H_5	C_6H_5	101–102[b]	$C_{18}H_{18}N_2O$	77.67	6.51	10.06	77.39	6.75	9.95
C_6H_5	CH_3	C_2H_5	CH_3	77–78[c]	$C_{14}H_{18}N_2O$	73.01	7.87	12.16	72.84	7.99	12.23
C_6H_5	C_6H_5	C_2H_5	C_6H_5	160–161[d]	$C_{24}H_{22}N_2O$	81.32	6.25		81.53	6.41	
—$(CH_2)_5$—		H	n-C_4H_9	Waxy solid[b]	$C_{13}H_{22}N_2O$	70.23	9.97	12.60	70.56	10.23	12.37
—$(CH_2)_5$—		H	C_6H_5	149–150[b]	$C_{15}H_{18}N_2O$	74.35	7.49	11.56	74.13	7.66	11.33
—$(CH_2)_5$—		CH_3	C_6H_5	83–84[b]	$C_{16}H_{20}N_2O$	74.96	7.85	10.93	74.67	7.90	10.69
—$(CH_2)_5$—		H	C_6H_5	105–106	$C_{15}H_{18}N_2S$	69.72	7.02	10.84	69.99	7.09	10.84
CH_3	$(CH_3)_2CH$	H	CH_3	118–120	$C_9H_{16}N_2S$	58.67	8.75		58.65	8.62	

[a] Recrystallized from methanol. [b] Recrystallized from benzene–petroleum ether (b.p. 30–60°). [c] Recrystallized from methylcyclohexane–benzene. [d] Recrystallized from benzene.

TABLE IIA

OXAZOLIDINES



						Analyses, %						
						Calcd.			Found			
R_1	R_2	R_3	R_4	B.p. (mm.) or m.p., °C.	Formula	C	H	N	C	H	N	Method
CH_3	CH_3	CH_3	CH_3	64 (2)	$C_8H_{14}N_2O$	62.30	9.15	18.17	62.36	9.12	18.45	*d*
CH_3	CH_3	CH_3	n-C_3H_7	90 (1)	$C_{10}H_{18}N_2O$	65.89	9.96		66.10	10.03		*d*
CH_3	CH_3	CH_3	n-C_4H_9	100 (2)	$C_{11}H_{20}N_2O$	67.30	10.27	14.27	67.36	9.87	14.31	*b*
CH_3	CH_3	CH_3	C_6H_5	146 (5)	$C_{13}H_{16}N_2O$	72.19	7.45	12.95	72.44	7.70	12.66	*b*
CH_3	CH_3	CH_3	4-Cl-C_6H_4	39–40[a]	$C_{13}H_{15}ClNO_2$	62.27	6.03		62.07	6.16		*d*
CH_3	CH_3	3-Cl-4-$CH_3C_6H_3$	C_2H_5	77–78[a]	$C_{15}H_{19}ClN_2O$	64.42	6.86	10.05	64.57	7.10	9.93	*b*
CH_3	$(CH_3)_2CH$	$(CH_3)_2CH$	C_2H_5	110–112 (3)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.71	10.96	12.44	*c*
CH_3	$(CH_3)_3C$	C_2H_5	C_2H_5	108 (2)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.39	10.66	12.36	*c*
CH_3	C_6H_5	C_2H_5	CH_3	142 (7)	$C_{14}H_{18}N_2O$	73.01	7.81	12.16	72.92	7.95	12.31	*b*
C_2H_5	C_2H_5	CH_3	n-C_4H_9	135 (2)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.75	10.80	12.58	*b*
C_2H_5	C_2H_5	$(CH_3)_2CH$	C_2H_5	110 (2)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.88	10.56	12.06	*c*
-$(CH_2)_5$-		CH_3	C_6H_5	87–88[a]	$C_{16}H_{20}N_2O$	74.96	7.86	10.93	74.85	7.96	10.79	*d*

[a] Recrystallized from methanol. [b] Prepared by distillation of the acetylenic urea. [c] Prepared by base closure of the acetylenic urea. [d] Prepared by acid closure of the acetylenic urea.

is similar to X rather than XI. It would also be expected that the salt character of X would move the chemical shifts downfield. It was, therefore, decided that II was the more logical structure. Chemical confirmation of this structure assignment was obtained by hydrogenating II to IVa which was identical with the material prepared from the amino alcohol (V) and *n*-butyl isocyanate.

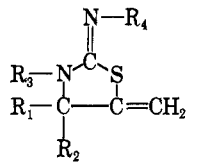
Treatment of the α,α-disubstituted acetylenic urea Ia with sodium ethoxide in ethanol resulted in a vigorous reaction which produced a new compound (VIa). The n.m.r. spectrum of this material showed a triplet at τ 6.69 (-N-CH_2-), an unsplit signal at 7.20 (-N-CH_3), additional butyl protons from 8.47 to 9.00, and an unsplit[8] signal at 6.11 assigned to the methylene protons. This compound was assigned the imidazolidinone structure, and confirmation was obtained by its independent synthesis from 3-methyl-3-methylamino-2-butanone (VII) and *n*-butyl isocyanate.

The extension of these reactions to variously substituted acetylenic amines was readily accomplished and the compounds which were prepared are reported in Tables I–III.

(8) The methylene protons of the imidazolidinones were not always a single peak. In fact, in 1-phenyl-3-methyl-4,4-pentamethylene-5-methylene-2-imidazolidinone, the n.m.r. spectrum contained two doublets with a difference in chemical shift of 11 c.p.s.

TABLE IIB

THIAZOLIDINES

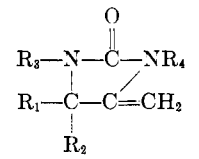


						Analyses, %						
						Calcd.			Found			
R_1	R_2	R_3	R_4	B.p. (mm.) or m.p., °C.	Formula	C	H	N	C	H	N	Method
CH_3	CH_3	H	CH_3	88 (5)	$C_7H_{12}N_2S$	53.83	7.74		53.75	7.92		*d*
CH_3	CH_3	H	n-C_4H_9	8.3 (0.05)	$C_{10}H_{18}N_2S$	60.56	9.15		60.47	9.07		*d*
CH_3	CH_3	CH_3	CH_3	118 (5)	$C_8H_{14}N_2S$	56.43	8.28	16.45	56.69	8.49	16.46	*d*
CH_3	CH_3	CH_3	C_6H_5	53–54[a]	$C_{13}H_{16}N_2S$	13.78[c]			13.52[c]			*d*
CH_3	CH_3	C_2H_5	n-C_4H_9	120 (5)	$C_{12}H_{22}N_2S$	63.66	9.80	12.38	63.42	9.98	12.03	*d*
—$(CH_2)_5$—		H	C_6H_5	174–177[b]	$C_{15}H_{18}N_2S$	69.72	7.02	10.84	69.42	6.98	10.64	*d*
—$(CH_2)_5$—		CH_3	C_6H_5	110–111[b]	$C_{16}H_{20}N_2S$	70.54	7.40	10.29	70.68	7.44	10.19	*d*

[a] Recrystallized from benzene–petroleum ether (b.p. 30–60°). [b] Recrystallized from methylcyclohexane–benzene. [c] Sulfur analysis. [d] Prepared by distillation of the acetylenic thiourea.

TABLE IIIA

IMIDAZOLIDINONES



						Analyses, %						
						Calcd.			Found			
R_1	R_2	R_3	R_4	B.p. (mm.) or m.p., °C.	Formula	C	H	N	C	H	N	Method
CH_3	CH_3	CH_3	C_2H_5	72 (1)	$C_9H_{16}N_2O$	64.25	9.59	16.65	63.54	9.56	16.25	*c*
CH_3	CH_3	CH_3	n-C_4H_9	102–105 (5)	$C_{11}H_{20}N_2O$	67.30	10.27	14.27	66.97	9.94	14.20	*c, d*
CH_3	CH_3	CH_3	C_6H_5	86–87[a]	$C_{13}H_{16}N_2O$			12.95			12.88	*c*
CH_3	CH_3	C_2H_5	4-Cl-C_6H_4	121–122[a]	$C_{13}H_{15}ClN_2O$	62.27	6.03	11.17	62.63	6.15	11.26	*c, e*
CH_3	CH_3	C_2H_5	C_2H_5	85 (0.1)	$C_{10}H_{18}N_2O$	65.89	9.96	15.37	65.68	9.94	15.09	*d*
CH_3	CH_3	C_2H_5	n-C_4H_9	102 (4)	$C_{12}H_{22}N_2O$	68.33	10.54	13.32	68.48	10.42	13.27	*d*
C_2H_5	C_2H_5	CH_3	n-C_4H_9	110 (5)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.48	10.75	12.60	*c*
C_6H_5	H	C_2H_5	C_6H_5	230 (1)	$C_{18}H_{18}N_2O$[f]	77.67	6.52		77.70	6.73		*c*
C_6H_5	CH_3	C_2H_5	CH_3	200 (1)	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.13	8.05	11.96	*c*
C_6H_5	C_6H_5	C_2H_5	C_6H_5	112[a]	$C_{24}H_{22}N_2O$	81.32	6.25	7.90	81.37	6.46	7.66	*c*
—$(CH_2)_5$—		H	C_6H_5	213–214[b]	$C_{15}H_{18}N_2O$	74.35	7.49	11.56	74.25	7.60	11.43	*c*
—$(CH_2)_5$—		CH_3	C_6H_5	120–121[a]	$C_{16}H_{20}N_2O$	74.96	7.86	10.93	75.02	8.06	10.76	*c*

[a] Recrystallized from benzene–petroleum ether (b.p. 30–60°). [b] Recrystallized from benzene–chloroform. [c] Prepared by base closure of acetylenic urea. [d] Prepared by dehydration of the ketourea. [e] Prepared by heating and distilling the acetylenic urea. [f] Double bond has shifted into ring: 3-ethyl-5-methyl-1,4-diphenylimidazolinone-2.

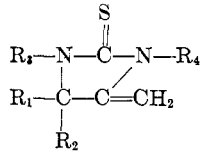
The difference in the structures of these products, compared with those reported by Yura[6a,b] for cyclization of mono α-substituted propargylureas, could be most readily explained by the steric effects of the groups substituted on the acetylenic amines. Therefore, it was of interest to examine various cyclizations of ureas in which steric effects could be expected due to the size of the different substituents.

From observations of the models of the imidazolidinones (VI) and the 2-iminooxazolidines (II), it would appear that large groups in R^1, R^2, R^3, and R^4 would inhibit the nitrogen closure to the imidazolidinone and in these cases the oxygen closure to the 2-iminooxazolidines would be favored. If the size of these groups is of sufficient importance, then, as they become large, the base-catalysis effect may be reversed. In order to test this possibility, the urea Ic [$R^1 = CH_3$; $R^3 = R^4 = C_2H_5$; $R^2 = C(CH_3)_3$] was subjected to the basic conditions which normally produce the imidazolidinones. In this example, only the 2-iminooxazolidine (IIc) was isolated, and no evidence for the presence of the imidazolidinone was seen. Therefore, it is apparent that the steric size of groups R^1, R^2, R^3, and R^4 does have an effect on the products obtained and that the larger these groups become the more difficult it is for an N-closure to take place.

It has been reported[7] that amides of substituted propargylamines cyclize to oxazolinium salts on treatment with acid. The ureas of propargylamines cyclize in the same manner and, upon neutralization of the resulting oxazolinium salts, the 2-iminooxazolidines, identical with those formed by thermal catalysis, are produced in 90–95% yields.

The only urea derived from an α-monosubstituted propargylamine which was investigated was that from the reaction of phenyl isocyanate with N-ethyl-α-phenylpropargylamine. In this instance, base closure produced 3-ethyl-5-methyl-1,4-diphenylimidazolinone-2. The double bond shifted into the ring from its exocyclic position.

TABLE IIIB
IMIDAZOLIDINETHIONES



						Analyses, %						
						Calcd.			Found			
R_1	R_2	R_3	R_4	B.p. (mm.) or m.p., °C.	Formula	C	H	N	C	H	N	Method
CH_3	CH_3	CH_3	CH_3	72–73[a]	$C_8H_{24}N_2S$	56.43	8.28		56.67	8.42		*d*
CH_3	CH_3	C_2H_5	C_4H_9	140 (10)	$C_{12}H_{22}N_2S$	63.66	9.80	12.38	63.84	10.22	12.29	*d*
—$(CH_2)_5$—		H	C_6H_5	248–250[b]	$C_{15}H_{18}N_2S$	69.72	7.02	10.84	69.99	7.09	10.89	*c*

[a] Recrystallized from benzene–petroleum ether (b.p. 30–60°). [b] Recrystallized from methylcyclohexane. [c] Prepared by base closure of acetylenic thiourea. [d] Prepared by dehydration of the ketothiourea.

The reaction of these propargylamines with isothiocyanates was also studied. It was very difficult to isolate a noncyclic product when a secondary propargylamine was treated with an isothiocyanate. Absence of the 3.03-μ band in the infrared spectrum assigned to the acetylenic ≡C—H bond and the appearance of bands at 6.10 and 6.18 μ of carbonyl intensity assigned to C=N and C=C, respectively, indicated that S-cyclization to the iminothiazolidines had occurred. This was confirmed by n.m.r. spectra. The thioureas from the primary propargylamines were more stable and could be isolated. They would undergo S-cyclization on standing. The freshly prepared thioureas from the primary amines could be cyclized to imidazolidinethiones by treatment with sodium ethoxide in alcohol. The 1,3-disubstituted imidazolidinethiones could be prepared by treating the appropriate amino ketone with the proper isothiocyanate.

The n.m.r. spectrum of 3,4,4-trimethyl-5-methylene-2-methyliminothiazolidine showed two doublets centered at τ 4.80 and 4.88 for the methylene protons. Other examples showed these doublets with greater or lesser difference in chemical shift and occasionally they appeared as an unsplit signal. However, they were always further downfield from that seen for the oxygen analog.

Treatment of the amino ketones (VII) with an isothiocyanate gave the hydroxyimidazolidinethiones (VIII) which could be readily dehydrated to the methylideneimidazolidinethiones (IX).

Experimental

All melting points were taken in open capillary tubes using a Culatti electrically heating air bath melting point apparatus.

Preparation of Ureas and Thioureas.—To a mixture of 0.1 mole of the substituted propargylamine in 100 ml. of ether, there was added slowly, with stirring, 0.12 mole of the isocyanate or isothiocyanate. The temperature was kept below 30°. After addition had been completed the mixture was stirred for an additional 0.5 hr., and the ether and excess isocyanate were removed at reduced pressure (below 30°). Yields were nearly quantitative in most cases.

Purification of the ureas was difficult since heating often caused cyclization. Some of the ureas could be recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°). See Table I for physical constants of the ureas and thioureas which were stable enough to purify or were analytically acceptable in their crude states.

Thermal Cyclization of Ureas.—The ureas were distilled under reduced pressure at temperatures above 80°. Some of the members of the series were converted to the cyclic forms by standing for several days at room temperature.

Physical properties of the compounds prepared by this method are designated by method *b* in Table IIA, and method *d* in Table IIB.

Base-Catalyzed Cyclization of Ureas and Thioureas.—A solution of sodium ethoxide (from 1 g. of sodium) in 100 ml. of ethanol was added slowly, with stirring, to 10 g. of the urea. The reaction was exothermic. The stirring was continued for 1 hr. and then 500 ml. of water was added. The solution was extracted three times with 100-ml. portions of ether; the ether layers were combined and dried over magnesium sulfate and concentrated at reduced pressure. The residue was purified either by distillation or by recrystallization. Yields were 80–90%. Compounds prepared in this manner are designated by method *c* in Tables IIA, IIIA, and IIIB.

Acid-Catalyzed Cyclization of Ureas and Thioureas.—A mixture of 10 g. of the urea in 50 ml. of concentrated hydrochloric acid was heated, with stirring, in a warm water bath. Indications of a reaction were darkening and evolution of fumes. The reaction was complete when all of the solid was in solution. After the addition of 50 ml. of water, the solution was neutralized with a saturated solution of sodium bicarbonate. The mixture was extracted with ether; the ether layer was dried and concentrated at reduced pressure. The residue was either distilled at reduced pressure or recrystallized from a suitable solvent. Yields in this reaction were 90–95%. Compounds prepared in this manner are designated by method *d* in Table IIA.

Preparation of Imidazolones and Imidazolidinethiones by Reaction of α-Amino Ketones with Isocyanates or Isothiocyanates.—To a well-stirred solution of 20 g. of the α-amino ketone in 150 ml. of ether there was added dropwise an equivalent amount of isocyanate or isothiocyanate. In most cases a layer of water formed during the addition. The solvent was distilled at reduced pressure and the residue was taken up in benzene. The mixture was refluxed for 4 hr. with use of a Stark and Dean trap to remove water. The solvent was distilled at reduced pressure and the products were purified by distillation or recrystallization. Yields were 80–95%. The physical constants are recorded in Tables IIIA and IIIB and identified by method *d*.

2-*n*-Butylimino-3,4,4,5-tetramethyloxazolidine. A. By Reduction.—A solution of 30 g. of 2-butylimino-5-methylene-3,4,4-trimethyloxazolidine in 150 ml. of ethanol was treated with hydrogen under approximately 40 p.s.i.g. of hydrogen using 5% palladium on carbon as catalyst. The mixture was filtered and the solution was concentrated at reduced pressure. The product distilled at 88–90° under 5 mm. of pressure, $n^{25}D$ 1.4610.

Anal. Calcd. for $C_{11}H_{22}N_2O$: C, 66.62; H, 11.18; N, 14.13. Found: C, 66.83; H, 11.37; N, 13.87.

B. From 3-Methyl-3-methylamino-2-butanol.—To a solution of 9 g. of 3-methyl-3-methylamino-2-butanol in 200 ml. of benzene there was added, slowly with stirring, 9 g. of *n*-butyl isocyanate. After the addition of 1 g. of *p*-toluenesulfonic acid the solution was refluxed for 16 hr. During this time the water from the reaction was collected in a Stark and Dean trap. The material was purified as in method A and was identical with the product obtained by method A.

3-Methyl-3-methylamino-2-butanol.—A solution of 12 g. (0.12 mole) of 3-methyl-3-methylamino-2-butanone[9] in 100 ml. of

(9) Prepared by the method of G. F. Hennion and P. E. Butler, *J. Org. Chem.*, **26**, 3341 (1961).

ethanol was hydrogenated over 5% palladium on carbon at approximately 40 p.s.i.g. of hydrogen. The product, 10 g. (83%), boiled at 95° at 70 mm.

Anal. Calcd. for $C_6H_{15}NO$: C, 61.49; H, 12.90; N, 11.95. Found: C, 61.53; H, 12.92; N, 11.85.

Acknowledgment.—The microanalyses were performed by Messrs. William Brown, Howard Hunter, George Maciak, David Cline, and Alfred Brown. Many of the starting materials were prepared in this laboratory by Dr. Dwight Morrison and Mr. Lawrence White. The infrared and n.m.r. spectra were obtained by Mr. John Klemm, Mrs. Doris Stephens, and Miss Martha Hofmann. The authors wish to thank especially Dr. Harold Boaz and Messrs. Paul Landis and Donald Woolf, Jr., for their invaluable services in interpreting and compiling the infrared and n.m.r. data.

The Light-Induced Amidation of Terminal Olefins[1]

DOV ELAD AND JOSHUA ROKACH[2]

Daniel Sieff Research Institute, The Weizmann Institute of Science, Rehovoth, Israel

Received January 8, 1964

The light-induced amidation of terminal olefins with formamide is described. The reaction can be performed both directly and through photochemical initiation by acetone. Yields of up to 90% of the 1:1 adducts are obtained.

Free-radical addition reactions to olefins are widely known in the literature.[3] These reactions have been found to involve a variety of reagents, including acetic, malonic, acetoacetic, and cyanoacetic esters.[4] The reactions are usually induced by initiators (mainly peroxides) or photochemically. Kharasch, Urry, and Kuderna[5] have shown that the addition of aldehydes to olefins to give the derived ketones can be induced by peroxides or light. This reaction, following the general scheme proposed for such additions, is described as a free-radical chain reaction. Similarly, methyl formate reacts with olefins in the presence of peroxides to give 1:1 adducts and higher telomers.[6] Urry and Juveland[7] have shown that amines add to olefins to give higher homologous amines derived by the substitution of alkyl groups for the hydrogen α to the amine group. Friedman and Shechter[8] found that substituted formamides undergo similar reactions with olefins in the presence of peroxides to give products resulting from the addition of both $\cdot CON(CH_3)_2$ and $HCON(CH_3)\dot{C}H_2$ radicals to the olefin.

A study of the addition of formamide to olefins was undertaken with the aim of finding a new process for converting olefins to higher amides, and possibly further to amines by reduction or by use of the Hofmann reaction. Since hydrolysis of the amides to the corresponding carboxylic acids can be effected by standard procedures, this reaction provides a new process for carboxylation of olefins under mild conditions at room temperature. Formamide, besides being a common reagent, has the advantage that its 1:1 adducts with olefins are highly crystalline solids which can be readily isolated.

(1) Presented before the XIXth International Congress of Pure and Applied Chemistry, London, July 10–17, 1963.

(2) In partial fulfillment of the requirements for a Ph.D. degree submitted to The Weizmann Graduate School in the Natural Sciences, 1962.

(3) For reviews see (a) J. I. G. Cadogen and D. H. Hey, *Quart. Rev.* (London), **8**, 308 (1954); (b) J. I. G. Cadogen, *Roy. Inst. Chem.* (London), *Lectures*, Monographs, Reports, No. 6 (1961).

(4) (a) J. C. Allen, J. I. G. Cadogen, B. W. Harris, and D. H. Hey, *J. Chem. Soc.*, 4468 (1962); (b) J. C. Allen, J. I. G. Cadogen and D. H. Hey, *Chem. Ind. (London)*, 1621 (1962).

(5) M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).

(6) W. H. Urry and E. S. Huyser, *J. Am. Chem. Soc.*, **75**, 4876 (1953).

(7) W. H. Urry and O. O. Juveland, *ibid.*, **80**, 3322 (1958).

(8) L. Friedman and H. Shechter, *Tetrahedron Letters*, **No. 7**, 238 (1961).

Results

The light-induced addition of formamides to terminal olefins has been reported by us in a preliminary communication.[9] We have since found that the reaction can be initiated photochemically by acetone, and the present paper includes full details of the reactions and the products obtained.

Formamide was found to add to olefins under photochemical conditions to give mainly the 1:1 adducts resulting from anti-Markovnikov addition.

$$RCH{=}CH_2 + H{-}CONH_2 \xrightarrow{h\nu} RCH_2CH_2CONH_2$$

R = alkyl, $H_3COOC(CH_2)_2$-, $H_2NOC(CH_2)_2$-, $H_3COOC(CH_2)_8$-, $H_2NOC(CH_2)_8$-

The acetone-initiated reactions produced even higher yields of these adducts and require shorter irradiation periods. The reactions studied and the main products obtained are summarized in Table I. The 1:1 adducts

TABLE I

ADDITION PRODUCTS OF FORMAMIDE AND OLEFINS[a]

(Initiated by Acetone)

Olefin	Product, 1:1 adduct (%)	Source of light
1-Hexene	Heptanamide (50)[b]	Sun
1-Heptene	Octanamide (57)	Sun
	(61)	Ultraviolet[c]
1-Octene	Nonanamide (62)	Sun
	(51)	Ultraviolet[c]
1-Decene	Undecanamide (67)	Ultraviolet[c]
Methyl 10-undecylenate	Methyl 11-carbamoylundecanoate (53)	Ultraviolet[c]
10-Undecylenamide	Dodecanediamide (90)	Sun
Methyl 4-pentenoate	Methyl 5-carbamoylpentanoate (61)	Sun
	(58)	Ultraviolet[c]
4-Pentenamide	Adipamide (77)	Sun

[a] The mole ratio of formamide–olefin in the experiments mentioned was 18:1. [b] Yields are based on the olefins employed. The conversions are nearly quantitative in most cases. [c] Hanau Q81 high pressure mercury vapor lamps fitted into Pyrex tubes were used as the radiation source for these acetone-initiated reactions.

(9) D. Elad, *Chem. Ind. (London)*, 362 (1962). While our work was in progress, A. Rieche, E. Schmitz, and E. Gründemann [*Angew. Chem.*, **73**, 621 (1961)] reported the addition of formamide to olefins in the presence of peroxides at elevated temperatures.