the pH values were determined, and the spectra were measured on a Beckman DK 2 recording spectrophotometer at room temperature in 1-cm. silica cells.

2-Hydroxy-3,4′-dimethoxychalcone (XIII).—(a) The chalcone XIII was synthesized by the following modification of Robinson's procedure.[21] A solution of potassium hydroxide (11.5 g.) in the minimum quantity of water was added to a solution of *o*-vanillin (7.6 g.) and *p*-methoxyacetophenone (8.3 g.) in ethanol (40 ml.). After 20 hr., water (250 ml.) and glacial acetic acid (35 ml.) were added. The yellow product was collected and recrystallized from acetone–methanol. The chalcone XIII separated as yellow, glistening plates, m.p. 141–142°.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.67; 2 MeO-, 21.8. Found: C, 71.7; H, 5.58; MeO-, 21.7.

Acetylation of the chalcone (0.5 g.) in acetic anhydride (5 ml.) and pyridine (6 drops) gave 2-acetoxy-3,4′-dimethoxychalcone which separated from methanol as very pale yellow prisms, m.p. 111°.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.9; H, 5.56; 2 MeO-, 19.0. Found: C, 70.1; H, 5.50; MeO-, 18.9.

(b) 8,4′-Dimethoxyflavylium chloride[22] was crystallized as orange needles from glacial acetic acid by the addition of ether. Aqueous citric acid–sodium phosphate buffer solution (pH 5.4, 300 ml.) was added to a solution of the flavylium salt (4.0 g.) in warm methanol (300 ml.). The cloudy, warm solution was allowed to cool slowly. The yellow crystalline product was collected and recrystallized from acetone–methanol. Yellow plates, m.p. 141–142°, undepressed on admixture with the synthetic chalcone XIII, were obtained (3.0 g.).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.67; 2 MeO-, 21.8. Found: C, 71.8; H, 5.62; MeO-, 21.8.

The *acetate* of the product, prepared as above, separated from methanol as pale yellow prisms, m.p. and m.m.p. with 2-acetoxy-3,4′-dimethoxychalcone, 111°.

2,2′-Dihydroxy-3-methoxychalcone (XV).—(a) Aqueous potassium hydroxide (50%, 10 ml.) was added to a solution of *o*-hydroxyacetophenone (7.0 g.) and *o*-vanillin (7.5 g.) in ethanol (25 ml.). The mixture was heated under reflux for 1 hr. and acidified with dilute acetic acid (300 ml.). The yellow product solidified when the aqueous suspension was washed with a little petroleum ether and ether. It crystallized from methanol as golden yellow, prismatic needles, m.p. 179–180°, which gave an intense brown color with ferric chloride in ethanol (1.65 g.).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.22; MeO-, 11.5. Found: C, 71.2; H, 5.25; MeO-, 11.8.

The chalcone (0.2 g.), acetic anhydride (2.0 ml.) and pyridine (4 drops) were allowed to react for 10 min. at room temperature. Water was added and the solid product was collected. Recrystallized from acetone–methanol, 2′-hydroxy-2-acetoxy-3-methoxychalcone (XVI) separated as yellow prisms, m.p. 164–165°. In methanolic ferric chloride the acetate gave an intense brown color.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.2; H, 5.16; 1 MeO-, 9.9. Found: C, 69.1; H, 5.13; MeO-, 10.5.

(b) 8-Methoxy-2′-hydroxyflavylium chloride[14] (8.0 g.) was added to boiling 0.1 *M* aqueous citric acid (500 ml.). The mixture was heated for 5 min., cooled, and filtered. The yellow product crystallized from acetone–methanol as yellow needles, m.p. 179–180°, undepressed on admixture with the synthetic chalcone (4.6 g.).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.22; 1 MeO-, 11.5. Found: C, 70.9; H, 5.21; MeO-, 12.0.

Monoacetylation of the product, as described above, gave an acetate, m.p. and m.m.p. with 2′-hydroxy-2-acetoxy-3′-methoxychalcone, 164–165°. With methanolic ferric chloride the acetate gave an intense brown color.

Acknowledgment.—The author is indebted to L. M. White and Miss G. Secor for the elemental analyses.

(21) R. Robinson, H. G. Crabtree, C. K. Das, W. Lawson, R. W. Lunt, P. H. Roberts, and P. N. Williams, *J. Chem. Soc.*, **125**, 207 (1924).

(22) D. A. Collins, F. Haworth, K. Isarasena, and A. Robertson, *ibid.*, 1876 (1950).

Reactions of Propargyl Alcohols and Propargylamines with Isocyanates

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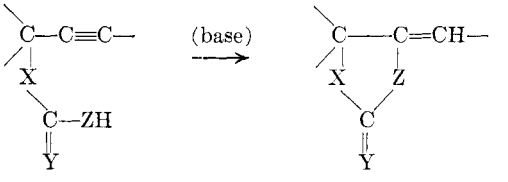
In the presence of a basic catalyst, propargyl alcohols and propargylamines react with isocyanates to give 4-methylene-2-oxazolidinones (IV) and 4-methylene-2-imidazolidinones (VIII), respectively. The expected open-chain urethanes (III) and ureas (VII) are obtained readily in the absence of base. The cyclizations are examples of especially easy intramolecular nucleophilic additions to C≡C.

The reaction of an ethynylcarbinol (I) and an isocyanate (II) in the presence of a catalytic quantity of a base does not stop with the formation of a urethane (III), but proceeds to give a 4-methylene-2-oxazolidinone (IV) by intramolecular N–H addition to the triple bond. In the absence of a basic catalyst, the expected urethane (III) is formed; the cyclization of III to IV occurs smoothly on treatment with sodium methoxide. This cyclization reaction was very recently reported in two brief notes.[1,2]

In this publication we wish to report our work relating to the synthesis of 4-methylene-2-oxazolidinones, as well as analogous cyclizations of propargylureas and propargyl *N*-phenylthiocarbamate. Reactions of this type represent especially easy intramolecular nucleophilic additions to C≡C, which might be formulated most generally as



Although urethanes can be obtained from tertiary alcohols only with great difficulty owing to facile dehydration to give an olefin and a urea, it has been shown that tertiary ethynylcarbinols undergo addition to isocyanates to afford the corresponding urethanes.[3] Carbamic acid esters have been synthesized from tertiary ethynylcarbinols by reaction with an alkali-metal cyanate and trichloroacetic acid.[4]

The 4-methylene-2-oxazolidinones (IV), described in Table I, were prepared by treatment of an ethynylcarbinol with an isocyanate and a catalytic amount of sodium methoxide. The structure IV was assigned on

(1) K. Sisido, K. Hukuoka, M. Tuda, and H. Nozaki, *J. Org. Chem.*, **27**, 2663 (1962).

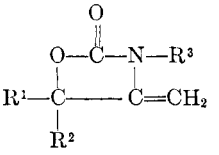
(2) N. R. Easton, D. R. Cassady, and R. D. Dillard, *ibid.*, **27**, 2927 (1962).

(3) H. Ensslin and K. Meier, U. S. Patent 2,798,885 (1957).

(4) G. Marshall, J. H. Barnes, and P. A. McCrea, U. S. Patent 2,814,637 (1957).

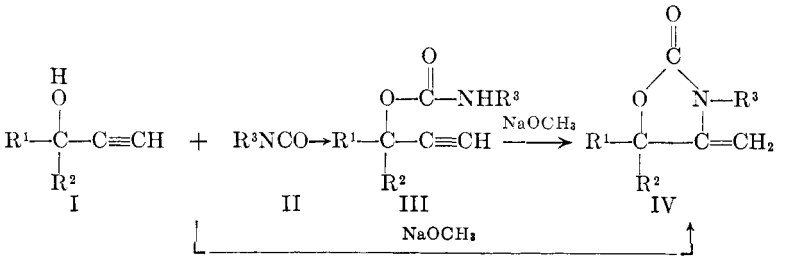
TABLE I

4-METHYLENE-2-OXAZOLIDINONES



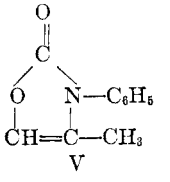
Compound	R¹	R²	R³	Reaction solvent	Approx. yield, %	Crystallization solvent	M.p., °C.	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	Mol. wt. Calcd.	Mol. wt. Found[a]
IVa	CH_3	CH_3	C_6H_5	N-Methylpyrrolidone	90	Ethanol	130–133[b]	70.9	71.0	6.45	6.67	6.90	7.14	203	204
IVb	—$(CH_2)_5$—		C_6H_5	N-Methylpyrrolidone	30–50	Ethanol	166–168[c]	74.1	73.8	7.12	7.05	5.77	5.61	243	243
IVc	H	H	C_6H_5	Ether	70	Chloroform Isoöctane	94–97[d]	68.6	68.4	5.18	5.04	8.00	8.15	175	177
IVd	CH_3	C_2H_5	C_6H_5	Cyclohexane	90	Pet. ether (30–60°)	87–89	—	—	—	—	—	—	—	—
IVe	CH_3	C_2H_5	p-ClC_6H_4	Ether	60	Ether	112–119[e]	—	—	—	—	—	—	—	—
IVf	CH_3	C_2H_5	2,5-$Cl_2C_6H_3$	Ether	50	1,2-Dimethoxyethane	134–135	—	—	—	—	—	—	—	—
IVg	CH_3	CH_3	C_2H_5	Ether	70	——[f]	——	61.9	61.9	8.38	8.45	9.03	9.02	—	—
IVh	CH_3	C_2H_5	C_2H_5	Ether	60	——[g]	——	63.9	63.4	8.87	8.86	8.28	8.43	—	—

[a] Ebullioscopic in acetone. [b] Reported,[2] m.p. 94–95°. We believe this reported m.p. to be in error. [c] Reported,[1] m.p. 167–167.5°. [d] Reported,[1] m.p. 97–98°. [e] Reported,[2] m.p. 121–122°. [f] Purified by distillation, b.p. 72–74° (0.3–0.6 mm.), $n^{25}D$ 1.4631. [g] Purified by distillation, b.p. 87–91° (1.2–1.5 mm.), $n^{25}D$ 1.4653.



the basis of analytical and infrared data. Characteristic infrared absorption bands were observed at 1775–1760 (C=O), 1695–1680, 1658–1635 (>C=CH_2), and 830–820 cm.$^{-1}$. The regions 3600–3100 and 2200–2000 cm.$^{-1}$ were devoid of significant absorption. In contrast, several urethanes (III), synthesized for comparison, exhibited the following infrared absorption pattern: 3460–3400 (N—H), 3330–3300 (≡C—H), 2140–2100 (C≡C), 1740 (C=O), and 1585 cm.$^{-1}$ (—CONH—). Although IVa and IVb did not undergo hydrogenation over a platinum oxide catalyst at room temperature under atmospheric pressure, they did absorb one mole of bromine readily. The addition of bromine to IIIa (R^1=R^2=CH_3; R^3=C_6H_5) and IIIb (R^1,R^2= —$(CH_2)_5$—; R^3=C_6H_5) was sluggish; however, the amount absorbed approached two moles. Quantitative hydrogenation of IIIa proceeded smoothly.

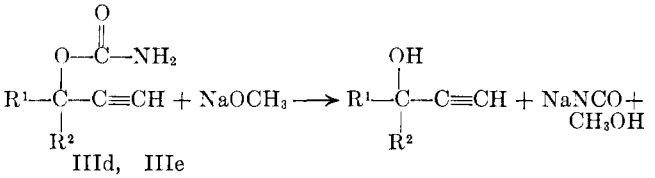
The structure of the major product of the base-catalyzed reaction of propargyl alcohol and phenyl isocyanate was shown to be 4-methylene-3-phenyl-2-oxazolidinone (IVc) by infrared and n.m.r. spectroscopy.[5] Its infrared spectrum showed a pattern identical with the other 4-methylene-2-oxazolidinones (IV) (1770, 1680, 1635, and 820 cm.$^{-1}$). Unequivocal confirmation of the position of the double bond in IVc was obtained from its n.m.r. spectrum, which displayed a band at τ 2.77 and two multiplets at τ 5.08 and τ 5.92, with intensity ratios of 5:2:2, respectively. The reaction afforded, in addition, small amounts of two other products, both isomeric with IVc, propargyl *N*-phenylcarbamate (IIIc) and 4-methyl-3-phenyl-4-oxazolin-2-one (V). The n.m.r. spectrum of V displayed a doublet at τ 8.25, a quartet at τ 3.33, and a multiplet at τ 2.77, with intensity ratios of 3:1:5, respectively. The olefinic carbon–carbon stretching frequency in the infrared spectrum of V appeared at 1670 cm.$^{-1}$; the carbonyl group absorbed at 1760 cm.$^{-1}$; the regions 1680–1695 and 800–900 cm.$^{-1}$ were devoid of significant absorption.



V

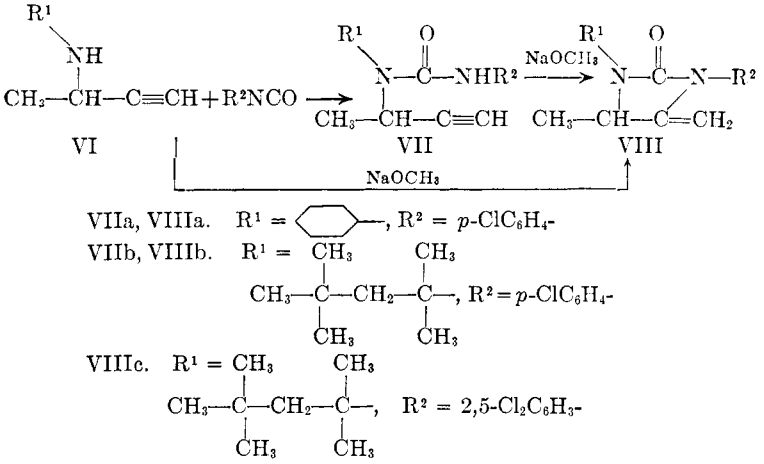
The carbamates IIId (R^1=CH_3, R^2=C_2H_5) and IIIe (R^1, R^2 = —$(CH_2)_5$—) did not undergo cyclization when treated with a catalytic amount of sodium methoxide. With a stoichiometric amount of base, cleavage occurred to the corresponding ethynylcarbinol and presumably cyanate.

(5) In view of the ease with which we were able to isolate IVc as the major product, it was surprising to note that Sisido, *et al.*,[1] found this product in one experiment, but could not isolate it in numerous experiments subsequently performed.



IIId, IIIe

Propargylic ureas (VII) were converted to 4-methylene-2-imidazolidinones (VIII) on contact with base. The ureas (VII) were synthesized from a 3-alkylamino-1-butyne (VI) and an isocyanate. When the latter condensation was conducted in the presence of sodium methoxide, the cyclic product VIII was obtained directly.



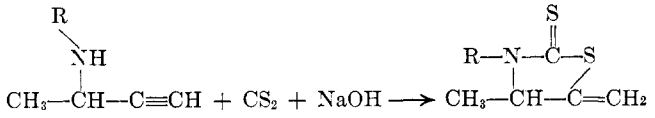
VIIa, VIIIa. R^1 = , R^2 = p-ClC_6H_4-

VIIb, VIIIb. R^1 = , R^2 = p-ClC_6H_4-

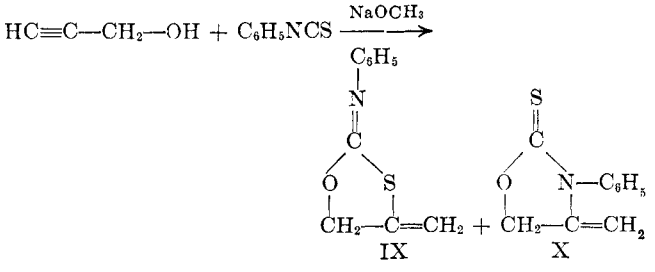
VIIIc. R^1 = , R^2 = 2,5-$Cl_2C_6H_3$-

The structural assignments for the ureas (VII) and the 4-methylene-2-imidazolidinones (VIII) were based on infrared spectral data and elemental analyses.

Even under forcing conditions, 3-*t*-octylamino-1-butyne (VIb) and 3-hydroxy-3-methyl-1-pentyne (I. R^1=CH_3, R^2=C_2H_5) resisted reaction with phenyl isothiocyanate. The amine VIb did not add to carbon disulfide as has been reported by Batty and Weedon[6] for certain less hindered 3-alkylamino-1-butynes.



A smooth reaction was observed, however, with propargyl alcohol and phenyl isothiocyanate. Two isomeric products, presumably IX and X, were isolated in 46 and 16% yield, respectively.



The structural assignments, though not unequivocal, were based on infrared, analytical and n.m.r. data. Both infrared spectra were devoid of C≡CH, N—H, and S—H absorptions. The lower melting compound, IX, was shown to be the stronger base by potentiometric titration with perchloric acid in acetic acid.

(6) W. Batty and B. C. L. Weedon, *J. Chem. Soc.*, 786 (1949).

The n.m.r. spectrum of IX contained multiplets centered at τ 5.17, τ 4.97, and τ 2.83, with intensity ratios of approximately 2:2:5, respectively; while X produced two quadruplets at τ 6.00 and τ 5.73 and two multiplets at τ 4.95 and τ 2.62, with intensity ratios of approximately 1:1:2:5, respectively. Minor absorption appeared in the CH_3 region in each spectrum (at τ 8.17 for X and τ 8.33 for IX), attributable to the presence of small amounts of the corresponding isomers having an internal double bond.

Experimental[7]

N.m.r. and Infrared Spectra.—The n.m.r. spectra were determined at 60 Mc. with a Varian HR-60 spectrometer. Deuteriochloroform was employed as the solvent and tetramethylsilane served as the internal standard.

The infrared spectra were obtained with a Perkin–Elmer, Model 21, spectrophotometer. Except where indicated otherwise, the compounds were scanned differentially in chloroform solution (0.1 g. compound/0.5 ml. $CHCl_3$). Matched 0.05-mm. cells (NaCl) were used.

1,1-Dimethyl-2-propynyl *N*-phenylcarbamate (IIIa).—To a solution of 16.8 g. (0.20 mole) of 2-hydroxy-2-methyl-3-butyne in 50 ml. of *N*-methylpyrrolidone was added 25.0 g. (0.21 mole) of phenyl isocyanate at a rate such that the temperature of the reaction mixture remained between 25 and 30°. The addition required about 3 hr. The mixture was stirred at room temperature for several hours and then was poured onto 200 g. of crushed ice. The product was extracted with ether and the ether solution was dried over anhydrous sodium sulfate. The ether was removed and the crude crystalline product (41 g.) was recrystallized from petroleum ether (30–60°), m.p. 102–103°; reported,[8] m.p. 101–101.5°. An acetylenic hydrogen analysis by the method of Barnes and Molinini[9] showed 0.20 g./meq. (calcd., 0.20 g./meq.). An ethanolic solution (25 ml.) containing 2.0 g. (0.00985 mole) of IIIa absorbed 0.0183 mole of hydrogen over a platinum oxide catalyst (0.05 g.) at room temperature under atmospheric pressure.

In a manner similar to that described above, **propargyl *N*-phenylcarbamate (IIIc)** was prepared from propargyl alcohol and phenyl isocyanate in an almost quantitative yield. Ether served as the reaction solvent; the product was purified by recrystallization from an ether–petroleum ether (30–60°) mixture, m.p. 61–63°; reported,[10] m.p. 62–63°.

1-Ethynylcyclohexyl *N*-phenylcarbamate (IIIb) was synthesized in a similar manner from phenyl isocyanate and 1-ethylcyclohexanol, m.p. 94–96° [from petroleum ether (30–60°)]; reported,[11] m.p. 94–96°.

Cyclization of 1,1-Dimethyl-2-propynyl *N*-Phenylcarbamate (IIIa).—A solution of 5.0 g. (0.025 mole) of IIIa and 0.08 g. (0.0015 mole) of sodium methoxide in 10 ml. of *N*-methylpyrroli-

(7) All melting points and boiling points are uncorrected.
(8) W. G. Young and I. D. Webb, *J. Am. Chem. Soc.*, **73**, 780 (1951).
(9) L. Barnes and L. J. Molinini, *Anal. Chem.*, **27**, 1025 (1955).
(10) R. Lespieau, *Bull. soc. chim. France*, (4) **3**, 640 (1908).
(11) K. Junkmann and H. Pfeiffer, U. S. Patent 2,816,910 (1957).

done was stirred at 70–75° for 2.5 hr. The red solution was kept at room temperature for several hours and then was poured into 50 ml. of cold water. The product, 5,5-dimethyl-4-methylene-3-phenyl-2-oxazolidinone (IVa), was collected on a filter and recrystallized from 95% ethanol, m.p. 130–133° (see Table I, footnote *b*); yield 4.4 g. (88%).

Direct Synthesis of the 4-Methylene-2-oxazolidinones (IV).—The following general procedure was used for the synthesis of the compounds described in Table I. The isocyanate was added slowly to a solution of the ethynylcarbinol and a catalytic amount of sodium methoxide (*ca.* 5 mole %) in the reaction solvent at 0–30°. The mixture was stirred at room temperature for several hours and then was added to an ice–water mixture containing just enough sulfuric acid to neutralize the base. The product was extracted with ether and the ether solution was dried over anhydrous sodium sulfate. The crude product, obtained on removal of the ether, was generally found to be of high purity by infrared examination and melting point determination. IVg and IVh were purified by distillation; the other compounds were recrystallized.

Base-catalyzed Reaction of Phenyl Isocyanate and Propargyl Alcohol.—During a period of 4.5 hr., 119 g. (1.0 mole) of phenyl isocyanate was added to a solution of 56 g. (1.0 mole) of propargyl alcohol and 1.8 g. of sodium methoxide in 300 ml. of diethyl ether while the temperature was maintained at 25–33°. After the mixture was heated under gentle reflux for 8 hr., the dark ether solution was decanted from a large quantity of crystalline solid which had precipitated.

The solid, which proved to be the major product, 4-methylene-3-phenyl-2-oxazolidinone (IVc), was recrystallized from a chloroform–isoöctane mixture; yield, 122 g. (See Table I). From the dark ether solution an oily mixture was obtained. Its infrared spectrum showed the presence of propargyl *N*-phenylcarbamate (IIIc). From the oil, 4-methyl-3-phenyl-4-oxazolin-2-one (V) was isolated by distillation, b.p. 135–140° (0.35 mm.), $n^{25}D$ 1.5583 (uncor.). On standing, the compound solidified. It was purified by recrystallization from an ether–petroleum ether (30–60°) mixture, m.p. 57–58°; reported,[1] m.p. 97.5–98°.[12]

Anal. Calcd. for $C_{10}H_9O_2N$ (V): C, 68.6; H, 5.18; N, 8.00; mol. wt., 175.2. Found: C, 68.5; H, 5.01; N, 8.09; mol. wt., (ebullioscopic in acetone), 176.

Bromination of IIIa, IIIb, IVa, and IVb.—A weighed quantity of the unsaturated compound was dissolved in chloroform. The solution was titrated with a standardized solution of bromine in chloroform to the appearance of a permanent yellow color. Difficulty was encountered with the propynyl compounds, IIIa and IIIb, owing to the appearance of a precipitate during the titration. The following results were obtained (compound, mol Br_2/mole): IIIa, 1.71; IIIb, 1.94; IVa, 1.00; IVb, 0.90.

Attempted Cyclizations of 1-Ethyl-1-methyl-2-propynyl Carbamate (IIId) and 1-Ethynylcyclohexyl Carbamate (IIIe).—The carbamates IIId and IIIe were prepared by the method of Marshall, Barnes, and McCrea.[4] A solution of 20.6 g. of IIId (m.p. 56–57°; reported,[4] m.p. 53.5–55°) and 0.1 g. of sodium methoxide in 40 ml. of *N*-methylpyrrolidone was stirred for 8 hr. at 60–70°. The mixture was poured into water and the product was extracted with ether. An infrared spectrum of the oil (16.1 g.), obtained from the ether solution, showed it to be mainly starting material.

A mixture of 0.12 mole of IIId and 0.12 mole of sodium methoxide in 50 ml. of ether was stirred at 30–35° for 1 hr. and then was allowed to remain at room temperature overnight. The slurry was poured into 200 ml. of cold water and the system was neutralized with 10% sulfuric acid. The liquid product (8.5 g.) was extracted with ether and the solution was distilled. Thus, 3.5 g. (30%) of 3-hydroxy-3-methyl-1-pentyne (b.p. 31–36° (12 mm), $n^{25}D$ 1.4282) and 2.5 g. (15%) of starting material, IIId, were obtained. Both compounds were identified by their infrared spectra.

Similarly, treatment of 5.0 g. of the carbamate IIIe (m.p. 94–95°; reported,[11] m.p. 94–96°) with 1.6 g. of sodium methoxide afforded 3.6 g. of an oil which consisted mainly of 1-ethynylcyclohexanol.

3-*t*-Octylamino-1-butyne (VIb) and 3-Cyclohexylamino-1-butyne (VIa).[13]—A mixture of 50 g. (0.39 mole) of *t*-octylamine (b.p. 137–143°), 50 g. of freshly distilled 1,2-dimethoxyethane and 5 g. (0.05 mole) of cuprous chloride was treated with acetylene under 400–450-p.s.i. pressure in a magnetically stirred autoclave. During a period of 26 hr. at 110–120°, 16 g. (0.615 mole) of acetylene was adsorbed. Distillation afforded, in addition to 3.0 g. (5.8%) of *t*-octylamine, 47.4 g. (67.2%) of pure 3-*t*-octylamino-1-butyne (VIb) b.p. 66° (4.0–4.5 mm.), $n^{25}D$ 1.4432. The infrared spectrum (liquid) showed absorption bands at 3320 (≡CH), 2990 (C—H), 2105 (C≡C), 1475 (CH_2), 1380, and 1370 cm.$^{-1}$ (C—CH_3). Apparently, the N—H absorption was too weak to be observed.

In an analogous manner, 3-cyclohexylamino-1-butyne (VIa) was prepared, b.p. 74–77°(10–12 mm.). The compound solidified at room temperature; reported,[13] b.p. 82–85° (17 mm.), 60° (5 mm.), m.p. 43–44°.

***N*-Cyclohexyl-*N*-(1-methyl-2-propynyl)-*N'*-*p*-chlorophenylurea (VIIa).**—A solution of 17 g. (0.11 mole) of *p*-chlorophenyl isocyanate in 30 ml. of ether was added to 13.8 g. (0.11 mole) of 3-cyclohexylamino-1-butyne (VIa) during a period of 0.75 hr. at 25–35°. An additional 300 ml. of ether was added to the gelatinous slurry and the heterogeneous mixture was stirred at room temperature for 5 hr. From the reaction mixture 11 g. of colorless crystalline product was removed directly by filtration. An additional 20 g. of crude solid was obtained from the ether solution. Purification was effected by recrystallization from an ether–petroleum ether (30–60°) mixture, m.p. 107–109°, yield 18.6 g. (60%).

Anal. Calcd. for $C_{17}H_{21}ON_2Cl$: C, 66.9; H, 6.90; N, 9.18; Cl, 11.65. Found: C, 67.0; H, 6.95; N, 8.98; Cl, 11.62.

Infrared absorptions: 3375 (N—H), 3290 (≡CH), 1663 (C=O), 1600 and 1497 (aromatic C=C), and 1530 cm.$^{-1}$ (—CONH—).

5-Methyl-4-methylene-3-*p*-chlorophenyl-1-cyclohexyl-2-imidazolidinone (VIIIa).—A solution of 5.0 g. (0.012 mole) of the urea VIIa in 20 ml. of *N*-methylpyrrolidone was treated with a few milligrams of sodium methoxide. An exothermic reaction which carried the temperature to 50° was observed. The red solution was heated at 50–60° for 4 hr., and then was poured into an ice–water mixture. The product was extracted with ether and the ether solution was dried over anhydrous sodium sulfate. An oil (5.0 g.) remained after removal of the ether. The product VIIIa was purified by crystallization from an ether–petroleum ether (30–60°) mixture, m.p. 147–151°, yield 2.6 g. (52%).

Anal. Calcd. for $C_{17}H_{21}ON_2Cl$: C, 66.9; H, 6.90; N, 9.18; Cl, 11.65. Found: C, 66.9; H, 7.10; N, 9.05; Cl, 11.62.

Infrared absorptions: 1690 (C=O), 1660 (>C=CH_2) 1600 and 1500 cm.$^{-1}$ (aromatic C=C). The strong sharp bands at 3375, 3290, and 1530 cm.$^{-1}$, present in the spectrum of VIIa, were completely absent in the spectrum of VIIIa.

***N*-*t*-Octyl-*N*-(1-methyl-2-propynyl)-*N'*-*p*-chlorophenylurea (VIIb).**—3-*t*-Octylamino-1-butyne (0.055 mole) was treated with *p*-chlorophenyl isocyanate (0.055 mole) in ether. Purification of the product, VIIb, was effected by recrystallization from petroleum ether (30–60°), m.p. 67–69° yield 13 g. (70%).

Anal. Calcd. for $C_{19}H_{27}N_2OCl$: C, 68.1; H, 8.11; N, 8.36; Cl, 10.6. Found: C, 67.9; H, 8.17; N, 8.06; Cl, 10.6.

The infrared spectrum of VIIb was very similar to that of VIIa.

5-Methyl-4-methylene-3-*p*-chlorophenyl-1-*t*-octyl-2-imidazolidinone (VIIIb).—The cyclization of VIIb was conducted exactly as described for VIIa. The product VIIIb was recrystallized from petroleum ether (30–60°), m.p. 124–127°.

Anal. Calcd. for $C_{19}H_{27}N_2OCl$: C, 68.1; H, 8.11; N, 8.36; Cl, 10.6; mol. wt. 334. Found: C, 68.0; H, 8.20; N, 8.20; Cl, 10.6; mol. wt. (ebullioscopic in acetone), 328.

Infrared absorptions: 1690 (C=O), 1655 (>C=CH_2), 1600' and 1500 cm.$^{-1}$ (aromatic C=C).

VIIIb was also prepared directly from 3-*t*-octylamino-1-butyne (VIb) (21 g.; 0.116 mole), *p*-chlorophenyl isocyanate (18 g.; 0.116 mole) and sodium methoxide (1.0 g.; 0.018 mole) in ether solution. From the crude oily product (26.3 g.) there was obtained 8.0 g. (38.1%) of unchanged VIIb by distillation. Recrystallization of the distillation residue from an ether petroleum ether (30–60°) mixture afforded 12.5 g. (32%) of VIIIb, m.p. 119–126°. Its infrared spectrum was identical with the spectrum of the analytic sample of VIIIb described above.

5-Methyl-4-methylene-3-(2,5-dichlorophenyl)-1-*t*-octyl-2-imidazolidinone (VIIIc).—This compound was prepared directly from 3-*t*-octylamino-1-butyne, 2,5-dichlorophenyl isocyanate and

(12) Both the melting point and the infrared bands, which Sisido, *et al.*,[1] give for V, correspond to our data for IVc. Their n.m.r. data, however, coincide with ours.

(13) C. Gardner, J. D. Rose, V. Kerrigan, and B. C. L. Weedon, *J. Chem. Soc.*, 780 (1949).

sodium methoxide, m.p. 84–86°, yield 25%. The infrared spectrum of VIIIc was essentially similar to those of VIIIa and VIIIb.

Base-catalyzed Reaction of Propargyl Alcohol with Phenyl Isothiocyanate.—During a period of 1.3 hr., a solution of 13.5 g. (0.1 mole) of phenyl isothiocyanate in 15 ml. of ether was added to a solution of 5.6 g. (0.1 mole) of propargyl alcohol and 0.1 g. of sodium methoxide in 50 ml. of anhydrous ether. Periodic cooling was needed to maintain the reaction temperature at 25–30° during addition. The mixture was stirred at room temperature for 2 days and then was added to 200 g. of water. The organic layer was dried over anhydrous sodium sulfate. An oil (15.5 g.) remained when the ether was removed. The products IX and X were separated by fractional crystallization from an ether–petroleum ether (30–60°) mixture. First there was obtained 3.0 g.(16%) of X which was purified by recrystallization from diethyl ether, m.p. 109–110°.

Anal. Calcd. for $C_{10}H_9OSN$: C, 62.9; H, 4.71; N, 7.34; S, 16.75; mol. wt. 191. Found: C, 62.8; H, 4.76; N, 7.47; S, 16.66; mol. wt. (ebullioscopic in acetone), 195.

Infrared absorptions: 1660 (>C=CH_2), 1600 and 1500 (aromatic C=C), 1455 (CH_2), 1400, 1340, 1165, 840 (>C=CH_2) 692 cm.$^{-1}$ (monosubstituted benzene).

IX was then isolated and purified by recrystallization from an ether–petroleum ether (30–60°) mixture, m.p. 45–47°.

Anal. Calcd. for $C_{10}H_9OSN$: C, 62.9; H, 4.71; N, 7.34; S, 16.75; mol. wt., 191. Found: C, 62.4; H, 4.89; N, 74.7; S, 16.41; mol. wt. (ebullioscopic in acetone), 200.

Infrared absorptions: 1675 (C=N), 1630 (>C=CH_2) 1600, and 1500 (aromatic C=C), 1455 (CH_2), 1400, 1340, 1115, 1040, 875 (>C=CH_2), 695 cm.$^{-1}$ (monosubstituted benzene).

A 0.20-g. sample of IX and X was titrated potentiometrically (crystal violet indicator also used) with 0.1 *N* perchloric acid in glacial acetic acid.[14] Compound IX required 8.1 ml. (Found, 4.1 meq./g.; Calcd., 5.2 meg./g.); compound X took less than 0.5 ml.

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(14) S. Siggia and H. J. Stolten, "An Introduction to Modern Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1956, p. 37.

Nystatin. III. Mycosamine: Preparation and Determination of Structure

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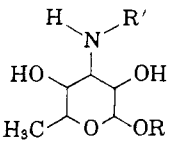
The preparation of mycosamine, the amino sugar component of nystatin and several other polyenic antifungal antibiotics, and of various derivatives is described. Periodate degradation has shown that mycosamine is a 3,6-dideoxy-3-amino-hexose belonging to the D-series.

In a preliminary communication[1] we have briefly presented the evidence which has let us assign structure I to mycosamine, the amino sugar obtained by hydrolysis of the antifungal antibiotics, nystatin and amphotericin B.[2] The present paper describes in detail the



I. R = R′ = H
II. R = H, R′ = $COCH_3$
III. R = H, R′ = $COOCH_2C_6H_5$
IV. R = CH_3, R′ = $COCH_3$
VII. R = CH_3, R′ = H + HCl
VIII. R = CH_3, R′ = C_2H_5

procedures used for the hydrolysis of nystatin, the isolation of the amino sugar, the preparation of its derivatives, and the degradation reactions by which its structure was established. The elucidation of its stereochemistry, as that of 3,6-dideoxy-3-amino-D-mannopyranose, by degradative means and its synthesis have been reported separately.[3,4]

Hydrolytic cleavage of amino sugar glycosides usually requires more vigorous conditions than that of ordinary glycosides because of the presence in the former of the positively charged amino group which shields the glycosidic linkage from the approach of the proton.[5] Conversion of the amino group to the neutral amido group by acylation restores normal susceptibility to hydrolysis to the glycosidic linkage.[6] Thus the cleavage of nystatin into mycosamine and aglycone was initially achieved by acetolysis (acetic acid, acetic anhydride, sulfuric acid), and the amino sugar moiety was isolated as the polyacetate. Subsequently, however, it was found that mycosamine could be cleaved from the nystatin molecule by vigorous aqueous acid hydrolysis or by methanolysis. It was possible in this manner to obtain mycosamine in the form of its hydrochloride or as the α-methyl glycoside hydrochloride. All these measures resulted in extensive degradation of the aglycone portion.

The analyses of several crystalline derivatives of mycosamine established the composition of the base as $C_6H_{13}NO_4$. No methoxy or N-methyl groups were present. One C-methyl group was demonstrable by the Kuhn–Roth determination, as well as by a positive iodoform reaction. Since in nystatin, as well as in mycosamine itself, the nitrogen atom is basic and reacts with ninhydrin, it must be present as a primary amino group. The observation that mycosamine is weakly but definitely reducing towards Tollen's and Fehling's reagents and gives a positive Morgan–Elson reaction indicated that it probably was a 6-deoxyaminoaldohexose. The absence of any absorption bands in the carbonyl region of the infrared spectrum suggested that a pyranose or furanose ring was present.

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