Acetylenic Amines. XI. Cyclizations of 3-Substituted N-(β-Hydroxyethyl)-1,1-dialkyl-2-propynylamines

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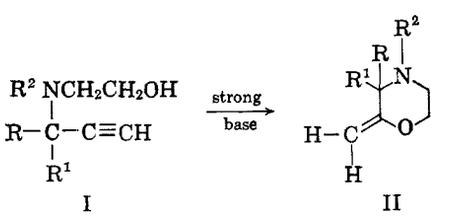
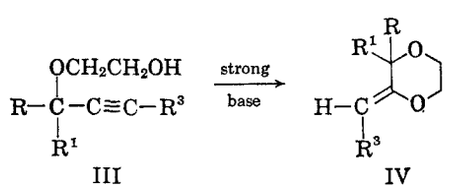
3-Alkyl-N-(β-hydroxyethyl)-1,1-dialkyl-2-propynylamines (VII), when treated with potassium hydroxide in an inert solvent, cyclized to 2,3,4,5-tetrahydro-1,4-oxazepines (VIII). Hydrogenation of VIII gave the hexahydro-1,4-oxazepines (XII). When the 3-substituent was chloro, phenyl, or methylthio, VII cyclized to a 2-methylenemorpholine XIII. The 3-pyrrolidinomethyl derivative VIIf gave a corresponding 2-(2-pyrrolidinoethylidene)-morpholine (XXIVc) when treated with base, whereas the methoxymethyl derivative gave the 1,4-oxazepine VIII. Possible mechanisms for these reactions are discussed.

The base-catalyzed cyclization of N-(β-hydroxyethyl)-2-propynylamines (I) to methylenemorpholines (II) has recently been reported.[1,2]

It has also been claimed that, under similar conditions, the hydroxyethyl derivatives of the 3-alkyl-2-propynyl alcohols (III) cyclize[3] to 1,4-dioxanes IV.



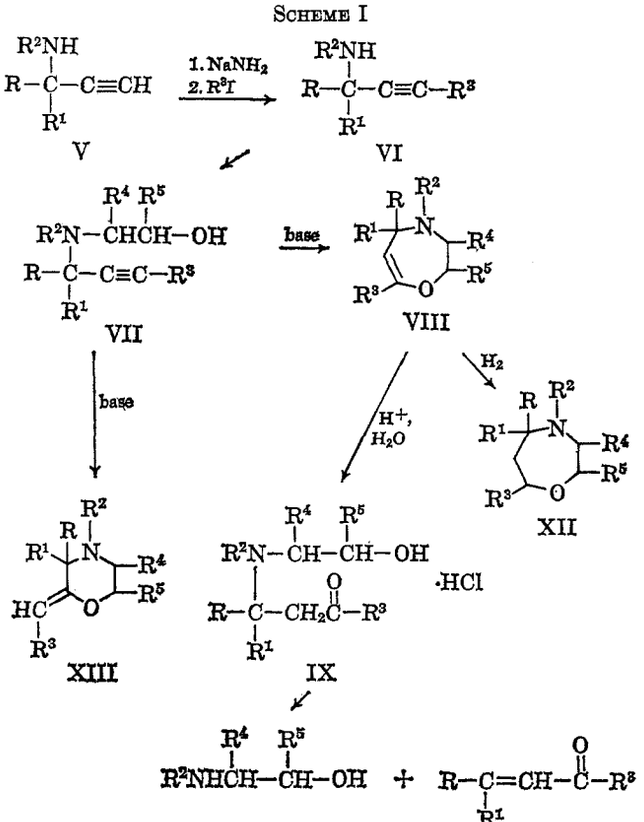


It has been reported in a preliminary communication[4] that cyclization of N-(β-hydroxyethyl)-N,1,1-trimethyl-2-butynylamine (VIIa, $R^3 = CH_3$) did not give the expected morpholine but gave instead the seven-membered ring VIIIa (4,5,5,7-tetramethyl-2,3,4,-5-tetrahydro-1,4-oxazepine).

The assignment of structure VIIIa was suggested from its n.m.r. spectrum. The protons on the methyl group in the 7-position and the vinyl proton were essentially unsplit.[5] This would not be consistent with the predicted ethylidenemorpholine spectrum. Chemical confirmation was obtained by an acid hydrolysis of VIIIa which gave mesityl oxide and N-methyl-β-hydroxyethylamine Xa, which would be expected only from the seven-membered ring (see Scheme I).

It has also been found that N-(2-hydroxy-2-phenylethyl)-N,1,1-trimethyl-2-butynylamine (VIIb) will cyclize to 4,5,5,7-tetramethyl-2-phenyl-2,3,4,5-tetrahydro-1,4-oxazepine (VIIIb). When VIIIb was treated with hydrochloric acid, N-methyl-N-(2-hydroxy-2-phenylethyl)amine hydrochloride (Xb) was formed.

SCHEME I



a, $R = R^1 = R^2 = R^3 = CH_3$; $R^4 = R^5 = H$

b, $R = R^1 = R^2 = R^3 = CH_3$; $R^4 = H$, $R^5 = C_6H_5$

This material would be expected from the decomposition of the unstable β-amino ketone IX, which would be obtained only in the case of the seven-membered ring (VIIIb).

This base-catalyzed cyclization was extended to other substituted N-(β-hydroxyethyl)-1,1-dialkyl-2-propynylamines (VII), where R^3 was methyl or ethyl. These compounds were prepared by the reaction of alkylene oxides (also styrene oxide) with the appropriately substituted 3-alkyl-2-propynylamines (VI), using methanol as the solvent. The 3-alkyl-2-propynylamines were obtained by the reaction of the sodium salts of the propynylamines (V) with an alkyl iodide[6] in liquid ammonia. In all cases, the substituted 2,3,4,5-tetrahydro-1,4-oxazepines (VIII) were obtained on treating VII with base (see Table I).

(1) A. T. Bottini, J. A. Mullikin, and C. J. Morris, *J. Org. Chem.*, **29**, 373 (1964).

(2) N. R. Easton, D. R. Cassady, and R. D. Dillard, *ibid.*, **28**, 448 (1963).

(3) W. J. Croxall and N. D. Dawson, U. S. Patent, 3,021,341 (Feb. 13, 1962).

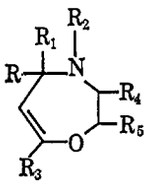
(4) N. R. Easton and R. D. Dillard, *Tetrahedron Letters*, **No. 26**, 1807 (1963).

(5) On the usual scan, splitting of these peaks is barely discernible. On an expanded frequency scale, the methyl group appears as a doublet centered at 103 c.p.s., and the vinyl proton as a quartet centered at 266 c.p.s. (J = 0.8–0.9 c.p.s.).

(6) G. F. Hennion and E. G. Teach, *J. Am. Chem. Soc.*, **75**, 4297 (1953).

TABLE I

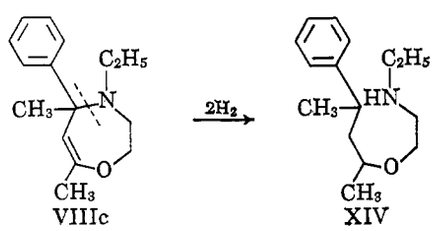
2,3,4,5,-TETRAHYDRO-1,4-OXAZEPINES



VIII

R	R^1	R^2	R^3	R^4	R^5	B.p., °C. (mm.)	$n^{25}D$	Formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found
CH_3	CH_3	H	CH_3	H	H	51 (6)	1.4674	$C_8H_{15}NO$	68.04	67.97	10.70	10.64
CH_3	CH_3	CH_3	CH_3	H	H	47–48 (4)	1.4689	$C_9H_{17}NO$	69.63	69.47	11.03	11.29
CH_3	CH_3	CH_3	CH_3	CH_3	H	55 (4)	1.4679	$C_{10}H_{19}NO$	70.95	71.08	11.31	11.48
CH_3	CH_3	CH_3	CH_3	H	CH_3	52 (4)	1.4610	$C_{10}H_{19}NO$	70.95	70.74	11.31	11.60
CH_3	CH_3	CH_3	CH_3	H	H	59 (4)	1.4666	$C_{10}H_{19}NO$	70.95	71.11	11.31	11.46
CH_3	CH_3	CH_3	$-CH_2OCH_3$	H	H	85 (4)	...	$C_{10}H_{19}NO_2$	64.83	64.64	10.34	10.47
CH_3	CH_3	H	CH_3	H	C_6H_5	77–79 (0.02)	...	$C_{14}H_{19}NO$	77.38	77.52	8.81	8.92
CH_3	CH_3	CH_3	CH_3	H	C_6H_5	76–77 (0.04)	...	$C_{15}H_{21}NO$	77.87	77.91	9.14	94.1
CH_3	C_6H_5	C_2H_5	CH_3	H	H	76–77 (0.01)	...	$C_{15}H_{21}NO$	77.87	77.91	9.14	9.25
$-(CH_2)_5-$			CH_3	CH_3	H	H	55 (0.04)	...	$C_{12}H_{21}NO$	73.79	73.94	10.73	10.96

Hydrogenation of VIII using palladium on carbon as the catalyst showed the absorption of 1 mole equiv. of hydrogen and gave the homomorpholines (XII) (see Table II). The infrared and n.m.r. spectra were consistent with these structures. 4-Ethyl-5,7-dimethyl-5-phenyl-2,3,4,5-tetrahydro-1,4-oxazepine (VIIIc), in which a tertiary benzylamine structure in the ring would be susceptible to hydrogenolysis, was hydrogenated in an attempt to obtain the oxazepine. However, hydrogenolysis occurred during hydrogenation to



VIIIc XIV

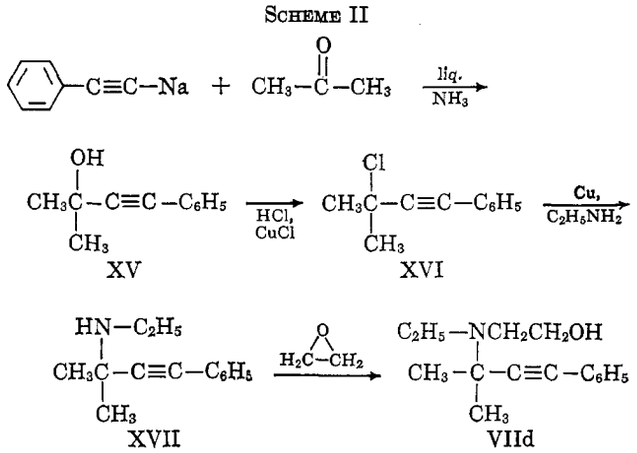
give the ring-opened product 2-(2-ethylaminoethoxy)-4-phenylpentane (XIV).

Since different products were obtained from the basic treatment of VII when R^3 was hydrogen and when R^3 was methyl, further study was initiated to determine the direction of the closure when R^3 was a group with different electronic character.

The 3-substituted N-(β-hydroxyethyl)-1,1-dialkyl-2-propynylamines used in this study, where R^3 = halogen,[7] methylthio,[8] or pyrrolidinomethyl,[9] were prepared using known procedures (see Experimental Section). To obtain the aryl-substituted acetylene, the sequence XV to VIId was followed. Although the yield in the replacement of the tertiary halogen with ethylamine, XVI → XVII, was only 10%, the fact that the reaction proceeded to this extent is interesting. The reaction of XVII with ethylene oxide gave 1-phenyl-N-ethyl-N-(β-hydroxyethyl)-1,1-dimethyl-2-propynylamine (VIId) (see Scheme II).

The cyclizations of the N-(β-hydroxyethyl)-1,1-dialkyl-2-propynylamines (VII), where the R^3 substituent was other than alkyl, were carried out in an inert solvent using powdered potassium hydroxide as the catalyst, and the products were isolated as clear distillates.

SCHEME II



XV XVI XVII VIId

Since there was a possibility of obtaining from the cyclization of VII either the six-membered ring, XIII, or the seven-membered ring, VIII, methods of distinguishing these materials were explored. The infrared spectra of both the six- and seven-membered rings had strong absorption peaks in the range of 6.0–6.14 μ, and, hence, it was not possible to distinguish between them by this method.

In the previously cited cases,[4] the n.m.r. spectra could be used to distinguish between six- or seven-membered rings because the protons of the alkyl group α to the vinyl proton would split this proton in the methylenemorpholine structure (XIII), but the absence of splitting of the vinyl (C-6) and 7-alkyl protons[5] would be seen in a seven-membered ring (see structures in Table III).

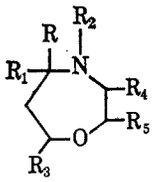
However, when there are no protons in the α-position of the substituents to be investigated, this portion of the n.m.r. spectra cannot be used to identify the product.

Further exploration of the n.m.r. spectra revealed that the ring methylene protons next to the nitrogen (b) in the six- and seven-membered rings differ in their

(7) C. W. Ryan, N. R. Easton, R. D. Dillard, and F. G. Henderson, *J. Med. Pharm. Chem.*, **5**, 780 (1962).
(8) M. Schmidt and V. Potschka, *Naturwissenschaften*, **50**, 302 (1963).
(9) G. F. Hennion and A. C. Perrino, *J. Org. Chem.*, **26**, 1073 (1961).

TABLE II

HEXAHYDRO-1,4-OXAZEPINES

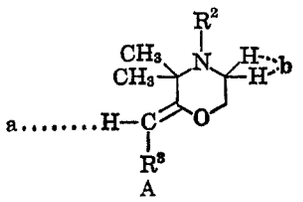


XII

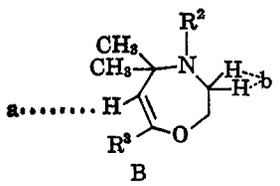
R	R^1	R^2	R^3	R^4	R^5	B.p., °C. (mm.)	$n^{25}D$	Formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found
CH_3	CH_3	H	CH_3	H	H	50 (6)	1.4479	$C_8H_{17}NO$	67.08	67.28	11.96	12.08
CH_3	CH_3	CH_3	CH_3	H	H	72.5 (20)	1.4490	$C_9H_{19}NO$	68.74	68.86	12.12	12.29
CH_3	CH_3	CH_3	CH_3	CH_3	H	56 (4)	1.4489	$C_{10}H_{21}NO$	70.12	69.95	12.35	12.41
CH_3	CH_3	CH_3	CH_3	H	CH_3	49 (4)	1.4448	$C_{10}H_{21}NO$	70.12	70.07	12.35	12.34
CH_3	CH_3	CH_3	C_2H_5	H	H	58–59 (4)	...	$C_{10}H_{21}NO$	70.12	69.88	12.35	12.08
CH_3	CH_3	CH_3	CH_2OCH_3	H	H	79 (4)	...	$C_{10}H_{21}NO_2$	64.13	64.37	11.30	11.59
CH_3	CH_3	H	CH_3	H	C_6H_5	77–80 (0.01)	...	$C_{14}H_{21}NO$	76.66	76.72	9.65	9.63
CH_3	CH_3	CH_3	CH_3	H	C_6H_5	82 (0.08)	...	$C_{15}H_{23}NO$	77.20	77.22	9.93	10.04
$-(CH_2)_5-$		CH_3	CH_3	H	H	56–57 (0.06)	...	$C_{12}H_{23}NO$	73.04	72.84	11.75	11.86

TABLE III

COMPARISON OF N.M.R. SPECTRA OF SIX- AND SEVEN-MEMBERED RINGS



A



B

Structure R^2	Structure R^3	A or B	Position of peaks assigned to proton a, c.p.s.	Center of peaks assigned to protons b, c.p.s.
CH_3	H	A	264	167
C_2H_5	H	A	267	166
C_2H_5	C_6H_5	A	372	169
C_2H_5	Cl	A	333	167
CH_3	$-SCH_3$	A	315	167
H	CH_3	B	271	183
CH_3	CH_3	B	266	184
CH_3	$-CH_2OCH_3$	B	282	186

chemical shifts.[10] For the six-membered rings, the protons appeared as multiple peaks centered in the range of 167–169 c.p.s., whereas, for the seven-membered series, they were centered at 183–186 c.p.s. (see Table II).

The n.m.r. spectra of the products obtained from the cyclizations where R^3 = phenyl, chloro, or methylthio, showed peaks centered at 167–169 c.p.s. for the ring N-methylene protons, and therefore, the methylenemorpholine structure XIII was assigned. However, the n.m.r. spectrum of the product from the cyclization of the methoxymethyl-substituted acetylene showed the peaks for the methylene group adjacent to the nitrogen atom centered at 186 c.p.s., and the seven-membered ring structure VIIIe was assigned. This was confirmed by the lack of splitting of the vinyl proton.

(10) The 60-Mc. n.m.r. spectra were obtained on a Varian Associates Model HR-60 in deuteriochloroform with tetramethylsilane as an internal standard or in deuterium oxide with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as the internal standard.

The products of chemical reactions provided further proof of structure for the phenyl-, chloro-, and methylthio-substituted methylenemorpholines XIII.

3,3,4-Trimethyl-2-phenylmethylenemorpholine (XIIIa) was hydrogenated in ethanol using palladium on carbon as catalyst, and the product was isolated as the hydrochloride. The n.m.r. spectrum was consistent with the morpholine structure but not for a seven-membered ring, which would have a proton on a carbon atom adjacent to a phenyl group and to an oxygen function, which would give multiple peaks centered at approximately 340 c.p.s. The absence of these peaks rules out the seven-membered ring.

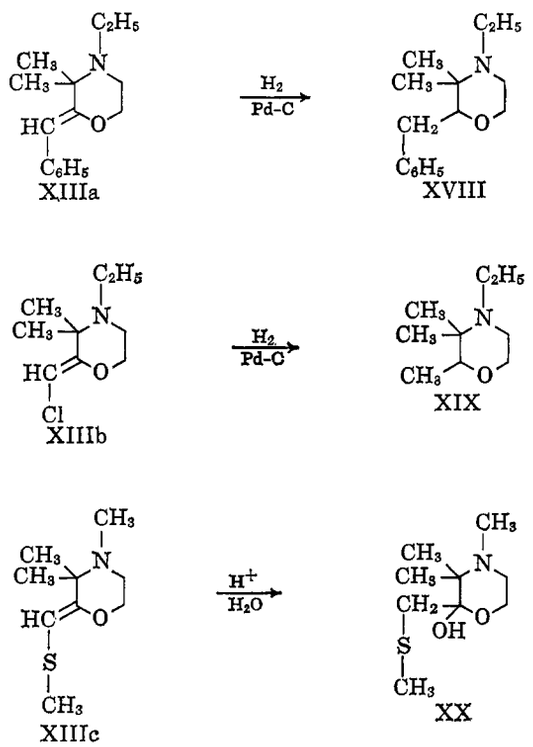
4-Ethyl-3,3-dimethyl-2-chloromethylenemorpholine (XIIIb)[2] was hydrogenated in ethanol using palladium on carbon as the catalyst. The chlorine atom was removed during hydrogenation to give the known 4-ethyl-2,3,3-trimethylmorpholine[2] isolated as the hydrochloride.

The methylthio derivative XIIIc was warmed overnight in 5% hydrochloric acid, the excess water was removed *in vacuo*, and a stable hydrated product (XX) was isolated as the hydrochloride. The infrared spectrum of XX showed hydroxyl absorption at 2.95 μ and no absorption in the 6-μ region. These data fit best the proposed structure XX, since the seven-membered ring structure would give a thiol ester, which would give carbonyl absorption in the infrared spectrum (see Scheme III).

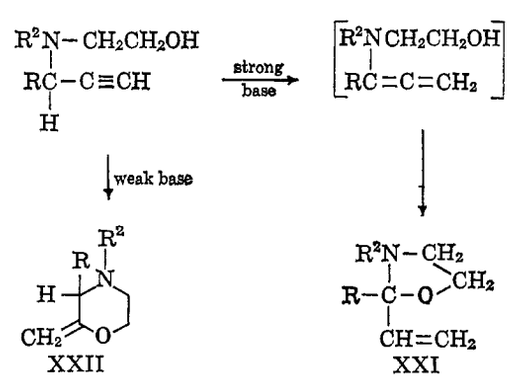
From the examples cited above, the influence of substitution on the acetylenic group of VII to intramolecular alkoxide ion addition is apparent, the alkyl substitution giving seven-membered rings and the phenyl, chloro, and methylthio substitutions giving six-membered rings (XIII). Seemingly, these observations relate only to the *inductive effect* of the substitution: electron-releasing groups lead to seven-membered rings while electron-withdrawing substituents give the six-membered rings. The distribution of charge in the transition state leading to closure of a six-membered ring is aided by the electron-withdrawing group at the terminal carbon.

The base-catalyzed cyclization of N-(β-hydroxyethyl)-4-pyrrolidino-N,1,1-trimethyl-2-butynylamine (VIIf) represents a special case in that it has protons α

SCHEME III



to the acetylenic group and to a nitrogen atom. Croxall and Mellema[11] have shown that N-(β-hydroxyethyl)-propargylamines, which also have protons α to the acetylenic group, cyclize to five-membered rings XXI on treatment with potassium hydroxide in toluene or xylene. Bottini, *et al.*,[1] have confirmed this observation and also have shown that, on treatment with weaker bases, the six-membered ring XXII is formed.

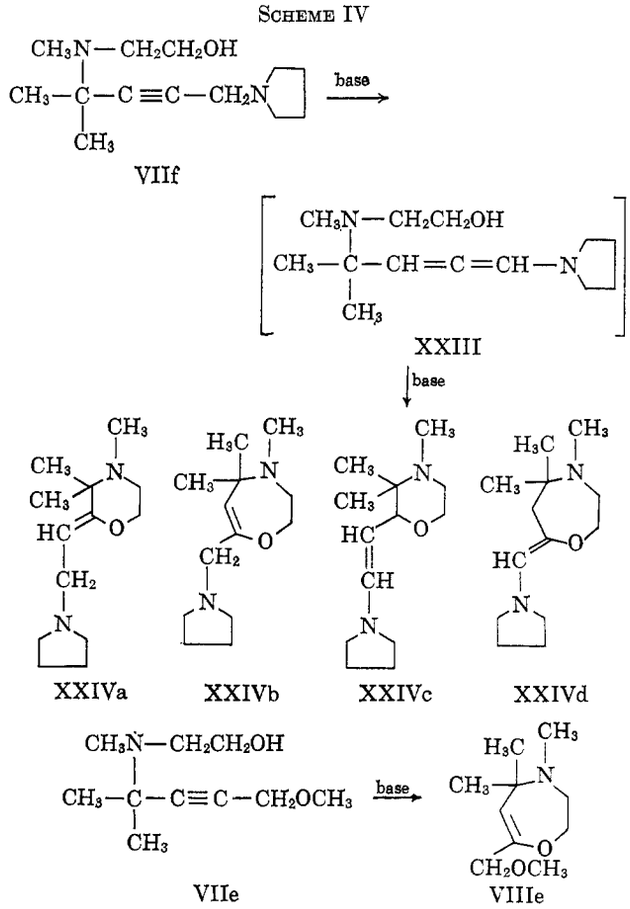


It has been suggested[1] that in the case of the propargylamine, the proton α to the acetylenic function and to the amino group is sufficiently acidic to be removed by the base and to give an allene structure. Cyclization by addition of the alkoxide ion to the allenic intermediate could give the five-membered ring XXI. Since the β-hydroxyethyl derivative of propargyl alcohol[3] closes to the six-membered ring IV (R = R^1 = R^3 = H), it appears that the acetylene–allene rearrangement is not involved in this case, and that cyclization involving nucleophilic addition to the triple bonds takes place.

(11) W. J. Croxall and J. H. Mellema, U. S. Patent 2,960,508 (Nov. 15, 1960).

From the above discussion it would appear that the ether VIIe and the amine analog VIIf cyclize by different mechanisms and that VIIe gives a seven-membered ring by addition to the acetylenic group, whereas VIIf produces the morpholine by cyclic addition to the allene. The cyclization of VIIf gave the morpholine XXIVc in which the vinyl group was α to the nitrogen instead of α to the oxygen. Although it is possible that a shift of the double bond could have occurred (XXIVa → XXIVc), the path of the reaction through the allene XXIII appears more logical and agrees with the mechanisms for the cyclizations cited above (see Scheme IV).

SCHEME IV



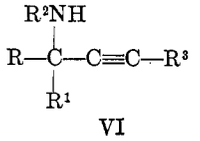
Confirmation of structure XXIVc was obtained from chemical reactions and from the n.m.r. spectrum. The cyclization product XXIV was found to undergo an enamine addition reaction with phenylacetylene using cuprous chloride as catalyst. Vinyl ethers of type XXIVa and XXIVb would not undergo this addition and thus were eliminated. The n.m.r. spectrum of XXIV showed a doublet centered at 378 c.p.s. (J = 14 c.p.s.), assigned to the vinyl proton on the carbon with the nitrogen group. No splitting should occur for this proton in XXIVd and thus structure XXIVc would appear to be the most logical.

Experimental Section

3-Alkyl-1,1-dialkyl-2-propynylamines (VI).—The 1,1-dialkyl-2-propynylamine (1.0 mole) dissolved in an equal volume of anhydrous ether was added dropwise to 1500 ml. of liquid ammonia to which had been added 1.0 mole of sodamide. After the addition was complete, 1 mole of the alkyl iodide (chloromethyl-methyl ether) dissolved in an equal volume of ether was added dropwise, and the liquid ammonia was replaced with ether over a 5-hr. period. To the ether mixture was added 1 l. of water, the

TABLE IV

3-SUBSTITUTED 1,1-DIALKYL-2-PROPYNYLAMINES



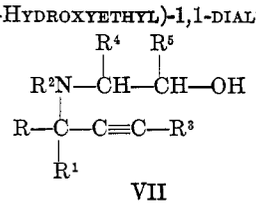
VI

R	R^1	R^2	R^3	B.p., °C. (mm.)	Formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found
CH_3	CH_3	H	CH_3	*a*	$C_6H_{12}ClN$	53.93	53.66	9.05	9.07
CH_3	CH_3	CH_3	CH_3	129 (740)	$C_7H_{13}N$	75.62	75.65	11.79	11.76
CH_3	CH_3	CH_3	C_2H_5	76–78 (75)	$C_8H_{15}N$	76.83	76.85	12.07	12.29
CH_3	CH_3	CH_3	$-CH_2OCH_3$	*b*	$C_8H_{16}ClNO$	54.08	53.81	9.07	9.33
CH_3	CH_3	CH_3	$-SCH_3$	56 (4)	$C_7H_{13}NS$	58.69	58.93	9.14	9.24
CH_3	CH_3	C_2H_5	C_6H_5	101 (4)	$C_{13}H_{17}N$	83.37	83.04	9.14	9.38
CH_3	C_6H_5	C_2H_5	CH_3	96–97° (4)	$C_{13}H_{17}N$	83.37	83.64	9.14	9.14
$-(CH_2)_5-$		CH_3	CH_3	64 (4)	$C_{10}H_{17}N$	79.40	79.66	11.34	11.57

[a] The hydrochloride was crystallized from methyl ethyl ketone, m.p. 183–185°. [b] The hydrochloride was crystallized from ethyl acetate, m.p. 93–95°.

TABLE V

3-SUBSTITUTED N-(β-HYDROXYETHYL)-1,1-DIALKYL-2-PROPYNYLAMINES



VII

R	R^1	R^2	R^3	R^4	R^5	B.p., °C. (mm.)	Formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found
CH_3	CH_3	H	CH_3	H	H	90 (4)	$C_8H_{15}NO$	68.04	67.84	10.70	10.79
CH_3	CH_3	CH_3	CH_3	H	H	77 (4)	$C_9H_{17}NO$	69.63	69.83	11.04	11.23
CH_3	CH_3	CH_3	CH_3	CH_3	H	78–79 (4)	$C_{10}H_{19}NO$	70.95	71.13	11.31	11.54
CH_3	CH_3	CH_3	CH_3	H	CH_3	72 (4)	$C_{10}H_{19}NO$	70.95	70.79	11.31	11.47
CH_3	CH_3	CH_3	C_2H_5	H	H	80 (4)	$C_{10}H_{19}NO$	70.95	71.05	11.31	11.32
CH_3	CH_3	CH_3	$-CH_2OCH_3$	H	H	110 (4)	$C_{10}H_{18}NO_2$	64.83	64.93	10.34	10.61
CH_3	CH_3	H	CH_3	H	C_6H_5	*a*	$C_{14}H_{19}NO$	77.37	77.44	8.81	8.88
CH_3	CH_3	CH_3	CH_3	H	C_6H_5	*b*	$C_{15}H_{22}ClNO$	67.27	67.44	8.28	8.38
CH_3	C_6H_5	C_2H_5	CH_3	H	H	96–97 (0.02)	$C_{15}H_{21}NO$	77.88	77.67	9.15	9.42
$-(CH_2)_5-$		CH_3	CH_3	H	H	80 (0.1)	$C_{12}H_{21}NO$	73.79	73.82	10.84	10.93
CH_3	CH_3	C_2H_5	C_6H_5	H	H	91 (0.01)	$C_{15}H_{21}NO$	77.88	78.03	9.15	9.12
CH_3	CH_3	CH_3	$-SCH_3$	H	H	67 (0.02)	$C_9H_{17}NOS$	57.72	57.50	9.14	9.22
CH_3	CH_3	CH_3		H	H	95–97 0.01	$C_{18}H_{24}N_2O$	69.60	69.80	10.78	10.74

[a] Crystallized from petroleum ether, m.p. 107–109° [b] The hydrochloride was crystallized from ethyl acetate, m.p. 125–127°.

ether layer was separated, dried over magnesium sulfate, and filtered, and the product was distilled (see Table IV). Yields of 70–80% were obtained.

3-Alkyl-N-(β-hydroxyethyl)-1,1-dialkylpropynylamine (VII).—To a solution of 0.5 mole of the 3-alkyl-1,1-dialkyl-2-propynylamine in 500 ml. of methanol was added 0.51 mole of the alkylene oxide. The solution was heated in an autoclave at 70° for 16 hr. and the product was distilled at reduced pressure (see Table V), giving 80–90% yields.

2,3,4,5-Tetrahydro-1,4-oxazopines (VIII).—The β-hydroxyethylamine VII (0.2 mole) was added dropwise to 250 ml. of refluxing xylene containing 10 g. of powdered potassium hydroxide, and after the addition was complete, the mixture was refluxed 4 hr. longer. After cooling to room temperature, the reaction mixture was washed with water and dried, and the xylene was removed by distillation. The remaining residue was distilled at reduced pressure (see Table I). Yields of 40–60% were obtained. Each product obtained was one-component material as was shown by its n.m.r. spectrum.

Reaction of VIIIa with Hydrochloric Acid.—VIIIa (35 g., 0.23 mole) was added dropwise to excess 20% hydrochloric acid and the solution was stirred for 2 hr. After the solution was made basic with excess 50% sodium hydroxide solution, it was extracted with ether. The ether solution was washed with excess dilute hydrochloric acid, dried over magnesium sulfate, filtered, and distilled. The fraction that boiled at 128–129° was collected, giving 14 g. (64%) of colorless oil. The infrared spectrum was identical with the spectrum of an authentic sample of mesityl oxide.

Anal. Calcd. for $C_6H_{10}O$: C, 73.42; H, 10.27. Found: C, 73.51; H, 10.16.

Hexahydro-1,4-oxazepines (XII).—The 2,3,5-tetrahydro-1,4-oxazepine (0.1 mole) was dissolved in 100 ml. of ethanol, and 2 g. of 5% palladium on carbon was added. The mixture was shaken with hydrogen under a pressure of 40 p.s.i. for 16 hr. at room temperature. After filtering, the ethanol was removed at reduced pressure and the product was distilled (see Table II), giving yields of 50–80%.

Reaction of 4,5,5,7-Tetramethyl-2-phenyl-2,3,4,5-tetrahydro-1,4-oxazepine (VIIIb) with Hydrochloric Acid.—To 3 g. of VIIIb in 150 ml. of methyl ethyl ketone was added 2 ml. of concentrated hydrochloric acid. The mixture was stirred 30 min. and all solvents were removed at reduced pressure. The residue was crystallized from methyl ethyl ketone, giving N-methyl-N-(β-hydroxy-2-phenylethyl)amine hydrochloride, m.p. 97–99°, as the product (30% yield).

Anal. Calcd. for $C_9H_{14}ClNO$: C, 57.60; H, 7.50. Found: C, 57.80; H, 7.48.

Treatment of 4-Ethyl-5,7-dimethyl-5-phenyl-2,3,4,5-tetrahydro-1,4-oxazepine (VIIIc) with Hydrogen.—The hydrogenation of VIIIc (11.5 g.) was performed in ethanol using palladium on carbon as catalyst as described for XII, and the product was distilled.

Eight grams (69% yield) of 2-(2-ethylaminoethoxy)-4-phenylpentane (XIV) boiling at 83° (0.88 mm.) was obtained, $n^{25}D$ 1.4888.

Anal. Calcd. for $C_{15}H_{25}NO$: C, 76.54; H, 10.71. Found: C, 76.62; H, 10.89.

3-Methylthio-N,1,1-trimethyl-2-propynylamine (VIa).—N,1,1-trimethyl-2-propynylamine (0.2 mole), dissolved in an equal volume of ether, was added dropwise to 500 ml. of liquid ammonium containing 0.22 mole of sodamide, and the mixture was stirred for 0.5 hr. Powdered sulfur (0.2 mole) was added in small portions, and stirring was continued for 1 hr. Methyl iodide (0.2 mole) dissolved in 50 ml. of ether was added dropwise, and the liquid ammonia was replaced with ether over a 2-hr. period. Water was added (cautiously at first), the ether layer was separated, dried over magnesium sulfate, and filtered, and the filtrate was distilled. Ten grams (35%) of product was obtained (see Table IV).

N-(β-Hydroxyethyl)-3-methylthio-N,1,1-trimethyl-2-propynylamine (VIIg).—Ethylene oxide (0.22 mole) and VIa (0.2 mole) were placed in 250 ml. of methanol and heated at 60° for 16 hr. The reaction mixture was distilled, giving 30 g. (80%) of clear distillate (see Table V).

N-(β-Hydroxyethyl)-4-pyrrolidino-N,1,1-trimethyl-2-butynylamine (VIIf).—N-(β-Hydroxyethyl)-N,1,1-trimethyl-2-propynylamine (0.2 mole), formaldehyde (0.33 mole), and 0.22 mole of pyrrolidine were placed in 60 ml. of dioxane and heated on a steam bath for 20 hr. Ether (0.5 l.) was then added, and the ether solution was washed with excess dilute hydrochloric acid. The aqueous solution was made basic with excess 50% sodium hydroxide solution, and the mixture was extracted with ether. After drying the ether solution over magnesium sulfate, it was distilled, giving 22 g. (50%) of product (see Table V).

N-Ethyl-3-phenyl-1,1-dimethyl-2-propynylamine (VIb).—To 100 g. of concentrated hydrochloric acid was added 22.2 g. (0.2 mole) of calcium chloride and 8 g. of cuprous chloride. After cooling to 0°, 32 g. (0.2 mole) of 1,1-dimethyl-3-phenyl-2-propyn-1-ol was added in small portions and the stirring maintained at 0° for 1 hr. The mixture was then extracted with ether, and the ether solution was washed with saturated potassium carbonate solution and with water. After drying over magnesium sulfate, the ether was evaporated and the residue was distilled at reduced pressure, giving 25 g. (70%) of 3-methyl-3-chloro-1-phenyl-1-butyne: b.p. 86–87° (4 mm.); infrared band at 4.5 μ (–C≡C–), no OH bands.

The crude chloroacetylene was added dropwise to 40 g. (0.6 mole) of 70% ethylamine containing 10 g. of copper powder and stirring was continued for 2 hr. The mixture was extracted with ether and the ether solution was extracted with dilute hydrochloric acid. The acid solution was made basic with 50% sodium hydroxide solution and extracted with ether, and the ether solution was dried over magnesium sulfate. After filtering, the ether was evaporated and the product was distilled at reduced pressure giving 3 g. (10%) of clear oil (see Table III).

N-Ethyl-3,3-dimethyl-2-phenylmethylenemorpholine.—N-(β-Hydroxyethyl)-N-ethyl-3-phenyl-1,1-dimethyl-2-propynylamine was cyclized as described for VIIIa and product was distilled, giving 7 g. (70%) of oil boiling at 80–82° (0.02 mm.). One-component material was obtained as indicated by its n.m.r. spectrum.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.87; H, 9.14. Found: C, 77.80; H, 9.16.

Similarly, VIIg was cyclized to **3,3,4-trimethyl-2-methylthiomethylenemorpholine (XIIIa)**, distilling at 105–107° (4 mm.), $n^{25}D$ 1.5307, giving a 70% yield.

Anal. Calcd. for $C_9H_{17}NOS$: C, 57.71; H, 9.14. Found: C, 57.86; H, 9.23.

3,3,4-Trimethyl-2-(2-pyrrolidinoethylene)morpholine.—N-(β-Hydroxyethyl)-4-pyrrolidino-N,1,1-trimethyl-2-butynylamine (0.1 mole) was added dropwise to 250 ml. of refluxing xylene containing 10 g. of powdered potassium hydroxide. The reaction mixture was maintained at reflux temperature for 4 hr. After cooling to room temperature, the mixture was filtered and the filtrate was distilled. The fraction boiling at 92–94° (0.008 mm.) was collected, giving 6 g. (30%) of clear oil.

Anal. Calcd. for $C_{13}H_{24}N_2O$: C, 69.59; H, 10.78. Found: C, 69.41; H, 10.94.

N-Ethyl-3,3-dimethyl-2-benzylmorpholine Hydrochloride (XVIII).—4-Ethyl-3,3-dimethyl-2-phenylmethylenemorpholine (0.02 mole) was hydrogenated in ethanol using palladium on carbon as catalyst at approximately 40 p.s.i. The catalyst was filtered and excess anhydrous hydrogen chloride was added. The ethanol and excess hydrogen chloride were removed at reduced pressure and the residue was crystallized from methyl ethyl ketone, giving 3 g. of the hydrochloride salt, m.p. 227–229°.

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.96. Found: C, 66.66; H, 8.88.

Hydrogenation of N-Ethyl-3,3-dimethyl-2-chloromethylenemorpholine (XIIIb).—Five grams of XIIIb was hydrogenated as described above, and the hydrochloride of the product, m.p. 190–192° (crystallized from ethyl acetate), was identical in all respects with the N-ethyl-2,3,3-trimethylmorpholine hydrochloride previously reported.[2]

Anal. Calcd. for $C_8H_{20}ClNO$: C, 55.80; H, 10.41. Found: C, 55.86; H, 10.29.

3,3,4-Trimethyl-2-hydroxyl-2-methylthiomethylmorpholine Hydrochloride (XX).—3,3,4-Trimethyl-2-methylthiomethylenemorpholine (6 g.) was refluxed 4 hr. in 250 ml. of 5% hydrochloric acid and then stirred overnight at room temperature. The water was removed at reduced pressure, and the residue was crystallized from methyl ethyl ketone, giving a white crystalline solid, m.p. 142–144° (4 g., 51% yield).

Anal. Calcd. for $C_9H_{20}ClNO_2S$: C, 44.70; H, 8.33. Found: C, 44.72; H, 8.39.

3,3,4-Trimethyl-2-(β-pyrrolidinoethyl)morpholine Dihydrochloride.—3,3,4-Trimethyl-2-(β-pyrrolidinoethylene)morpholine was hydrogenated as described for XVIII and the product was isolated as the dihydrochloride. After recrystallizing from isopropyl alcohol–ether, the hygroscopic white crystalline material melted at 240–242°.

Anal. Calcd. for $C_{13}H_{28}Cl_2N_2O$: C, 52.17; H, 9.43. Found: C, 51.96; H, 9.58.

3,3,4-Trimethyl-2-(4-phenyl-2-pyrrolidino-3-butynyl)morpholine Dihydrochloride.—The enamine XXIVc (0.01 mole) and phenylacetylene (0.015 mole) were placed in a flask and with stirring, 0.5 g. of cuprous chloride was added. The temperature rose to 48° and then cooled to room temperature over a 2-hr. period. The mixture was taken up in ether and extracted with dilute hydrochloric acid; the aqueous layer was made basic with sodium hydroxide solution and extracted with ether. The ether solution was dried over magnesium sulfate and filtered, and the ether was removed from the filtrate. The dihydrochloride, m.p 255–257°, of the remaining residue was made and crystallized from methyl ethyl ketone.

Anal. Calcd. for $C_{21}H_{32}Cl_2N_2O$: C, 63.15; H, 8.07. Found: C, 63.27; H, 8.33.

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