The double chloride of Vasicinone and platinum was prepared as above using Vasicinone hydrochloride (0.1 g.) and platinic chloride (0.095 g.). The crude substance was crystallized from 2% hydrochloric acid.

Anal. Calcd. for $B_2.H_2PtCl_4$: Pt, 23.9; Found: Pt, 23.9.

Acknowledgment.—The authors are indebted to Dr. A. H. Amin, Director of Research, Alembic Chemical Works Co. Ltd., for his kind interest and encouragement.

Acetylenic Amines. V. Morpholines from Substituted N-(2-Hydroxyalkyl)-propargylamines

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Various methods of preparing substituted N-(2-hydroxyalkyl)propargylamines and their cyclization and subsequent hydrogenation to various morpholine derivatives are reported. Facile hydration of 2-methylenemorpholines to the 2-hydroxy-2-methylmorpholines has been noted.

The base-catalyzed cyclization of N-(2-hydroxyalkyl)propargylamines (III. $R^1 = R^3 = H$) has been reported[1] to give oxazolidines (IV) instead of the expected morpholines (V). In our laboratories, however, it has been possible to prepare the morpholines (V) from compounds of the type III where both R and R^1 are alkyl or aryl, as shown in Fig. 1.

The ready availability[2,3] of the 1,1-disubstituted propargylamines (I) suggested their use as starting materials. It was found that they could be converted to the desired β-amino alcohols (III) by several methods. The reactions of I with ethylene oxide and substituted ethylene oxides could usually be accomplished, although the conditions necessary for the reactions to proceed needed to be varied. Since the reaction of substituted ethylene oxides always gave the 2-substituted-2-hydroxyethylamines (III), 1-substituted 2-hydroxyethylamines were obtained by the treatment of the amines with the appropriate α-halo ketones or esters followed by reduction with sodium borohydride or lithium aluminum hydride. Under the proper conditions, the reduction of the esters or ketones with lithium aluminum hydride or sodium borohydride proceeded with little or no attack at the acetylenic group.

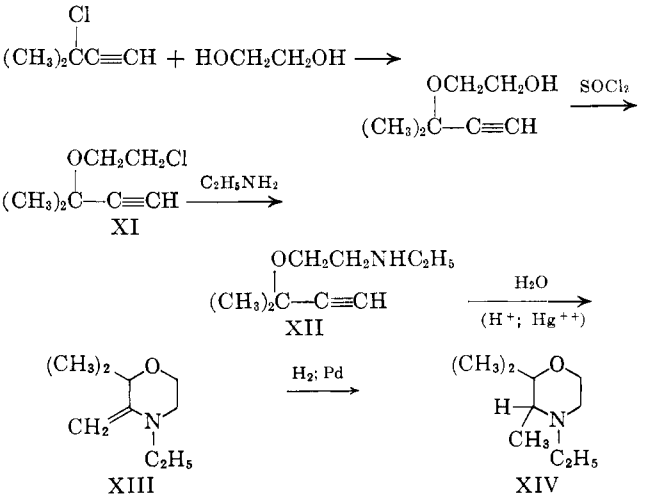
The base-catalyzed cyclization of these β-amino alcohols, where both R and R^1 are alkyl or aryl, gave the 2-methylenemorpholines (V) which could be readily hydrogenated to the 2-methylmorpholines (X). Treatment of V with dry hydrogen chloride under anhydrous conditions gave the hydrochloride salts. However, in the presence of water, hydration took place, and the 2-hydroxy-2-methylmorpholine (VI) was produced.

This compound (VI) was identical to that obtained by the treatment of the substituted N-(2-hydroxyalkyl)propargylamines (III) under conditions necessary for hydration[3] of the acetylenic amine.

The structure assigned to X was proved by an unequivocal synthesis. The β-hydroxyethylamine (VIII) was treated with ethylene oxide to form the aminodiol (IX). Cyclization of this compound under acidic conditions gave a compound identical to that obtained by hydrogenation of the 2-methylenemorpholine. Reduction of the 2-hydroxymorpholine (VI. $R = R^1 = CH_3$; $R^2 = C_2H_5$), with lithium aluminum hydride gave as one of the products a compound identical to the aminodiol (IX).

Substitution of chlorine for the terminal acetylenic hydrogen did not prevent cyclization since 1-chloro-3-(N-ethyl-N-2-hydroxyethylamino)-3-methyl-1-butyne[4] cyclized to the 2-(chloromethylene)morpholine.

For comparison purposes, the isomer XIV was prepared by means of the hydrogenation of XIII. Compound XIII was obtained by the acid-catalyzed cyclization of XII, which could be readily prepared from the chloro compound XI, as shown above.



The infrared and n.m.r. spectra were consistent with the assigned structures. The 2-methylenemorpholines gave intense absorption peaks in the infrared at 6 μ.

The stereochemistry of the hydroxymorpholines (VI), the morpholines (X), and the diols (IX), where $R \neq H$ or $R' = R$, has not been elucidated. The products, as isolated, appeared to be relatively pure materials and no evidence of isomers was encountered. The question of whether the same or different isomers of IX and X are produced by the different synthetic routes is being investigated.

(1) W. S. Croxall, N. D. Dawson, P. D. Arseneau, J. H. Mellema, and J. Mirya, 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960, Abstracts, p. 77P.

(2) G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, **82**, 4908 (1960).

(3) N. R. Easton, R. D. Dillard, W. J. Doran, Mabel Livezey, and D. E. Morrison, *J. Org. Chem.*, **26**, 3772 (1961).

(4) C. W. Ryan, N. R. Easton, R. D. Dillard, and F. G. Henderson, *J. Med. Pharm. Chem.*, **5**, 780 (1962).

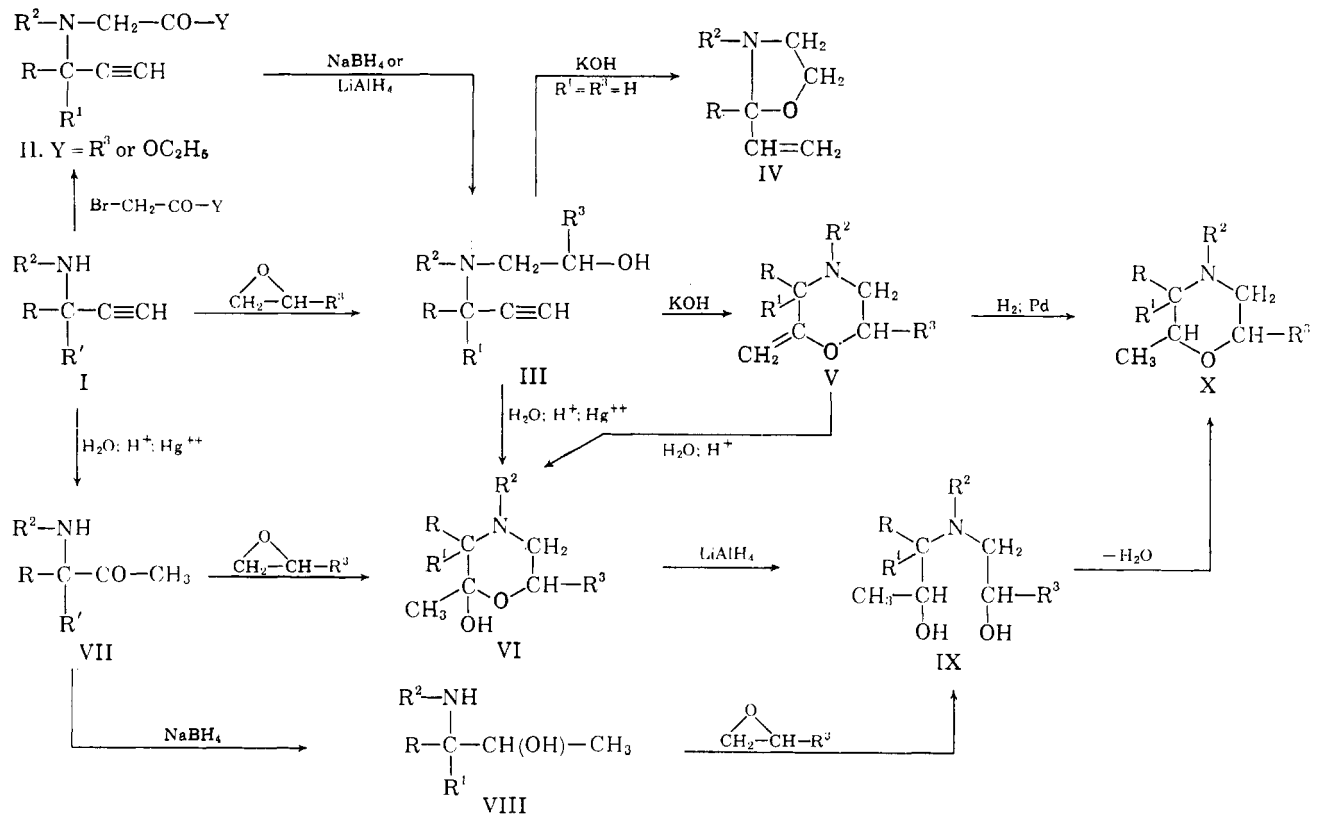


Fig. 1. Syntheses of polysubstituted morpholines.

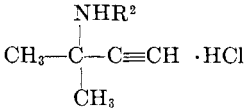
Experimental

Melting points are not corrected and were taken in open capillary tubes. No efforts to obtain maximum yields were made.

1,1-Disubstituted Propargylamine (I).—All acetylenic amines were prepared from the properly substituted acetylenic chlorides by the methods previously described.[2,3] New compounds are listed in Table I.

TABLE I

ACETYLENIC AMINES



R²	M.p.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
p-$CH_3C_6H_4$	158–159°	$C_{12}H_{16}ClN$	68.72	68.61	7.69	7.66
o-ClC_6H_4	128–129°	$C_{11}H_{13}Cl_2N$	57.41	57.36	5.69	5.99
m-ClC_6H_4	158–159°	$C_{11}H_{13}Cl_2N$	57.41	57.52	5.69	5.95
o-CH_3O-C_6H_4	[a]	$C_{12}H_{15}NO$	76.15	76.30	7.99	8.05
m-$O_2NC_6H_4$	[b]	$C_{11}H_{12}N_2O_2$	64.69	64.47	5.92	6.16
o-H_2N-C_6H_4	[c]	$C_{11}H_{14}N_2$	75.82	75.57	8.10	7.92
p-$(CH_3)_2$-NC_6H_4	175–177° (dec.)	$C_{13}H_{20}Cl_2N_2$	56.73	56.81	7.32	7.70
3-Cl-4-$CH_3C_6H_3$	150–151°	$C_{12}H_{15}Cl_2N$	59.03	59.31	6.19	6.36
$C_6H_5(CH_2)_2$	187–188°	$C_{13}H_{18}ClN$	69.78	69.73	9.15	9.01

[a] Free base, b.p. 130° at 0.5 mm. [b] Free base, b.p. 85° at 0.04 mm. [c] Free base, b.p. 108° at 4 mm.

N-(2-Hydroxyalkyl)propargylamines (III) (Table III).—The N-(2-hydroxyalkyl)propargylamines were prepared from the propargylamines by one or more of the three following methods.

(a) **With Ethylene Oxides.**—One mole of the propargylamine and 1.2 moles of the ethylene oxide were dissolved in 500 ml. of methanol and heated overnight in an autoclave at 70°. (The cyclohexene oxide reaction was heated for 72 hr.) Dry hydrogen chloride was added to the solution until it was acidic, and the methanol was removed under reduced pressure. The residue was dissolved in 300–400 ml. of water, washed with 500 ml. of ether, and the aqueous solution made strongly basic with 50% sodium hydroxide solution. The mixture was extracted with ether, the organic layer was dried over magnesium sulfate, filtered, and the ether removed from the filtrate. The residue was distilled under reduced pressure. The hydrochloride was prepared and recrystallized from ethyl acetate or methyl ethyl ketone. Yields of 50–80% were obtained.

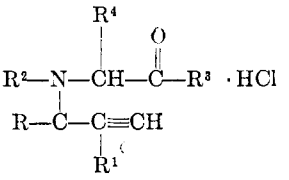
(b) **With α-Bromoacetophenones.**—A mixture of 1 mole of the propargylamine and 0.5 mole of the α-bromoacetophenone in 1 l. of acetonitrile was stirred overnight, and then dry hydrogen chloride was added until the mixture was acidic to Congo Red. The acetonitrile was removed under reduced pressure and the residue taken up in a mixture of water and ether. The aqueous layer was separated, made basic with 50% sodium hydroxide solution, and extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and the ether removed. The residue was distilled at reduced pressure (Table II).

To a solution of the N-phenacylpropargylamine (0.1 mole) in 200 ml. of methanol (cooled in an ice bath) there was added, in small portions, 0.2 mole of sodium borohydride. The resulting mixture was allowed to stand at 25° for 2 hr. Water (200 ml.) was added, and the mixture was stirred for 0.5 hr. and extracted with ether. The ether solution was dried over magnesium sulfate and filtered. The solvent was removed from the filtrate, and the residue was then distilled at reduced pressure or recrystallized. Over-all yields of 10–25% were obtained.

(c) **With Ethyl α-Bromopropionate: 3-[N-(1-Methyl-2-hydroxyethyl)ethylamino]-3-methyl-1-butyne.**—A mixture of 90 g. (0.5 mole) of ethyl α-bromopropionate and 111 g. (1.0 mole) of 3-(N-ethylamino)-3-methyl-1-butyne in 500 ml. of acetonitrile was refluxed for 48 hr., cooled, and dry hydrogen chloride was added until the mixture was acidic. The acetonitrile was then distilled and the residue taken up in a mixture of water and ether. The aqueous layer was separated, made strongly basic with 50% sodium hydroxide solution, and the product was extracted into ether. This solution was dried over magnesium sulfate, filtered,

TABLE II

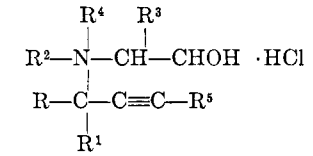
AMINO KETONES



R	R^1	R^2	R^3	R^4	M.p.	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found
CH_3	CH_3	C_2H_5	CH_3	H	126–128°	$C_{10}H_{18}ClNO$	58.96	59.16	8.91	9.07
CH_3	CH_3	CH_3	C_6H_5	H	150–152°	$C_{14}H_{18}ClNO$	66.79	66.68	7.21	6.97
CH_3	CH_3	C_2H_5	C_6H_5	H	189–190°	$C_{15}H_{20}ClNO$	67.78	67.50	7.59	7.43
CH_3	CH_3	CH_3	p-ClC_6H_4	H	214–216°	$C_{14}H_{17}Cl_2NO$	58.75	58.94	5.99	6.11
CH_3	CH_3	CH_3	p-$CH_3OC_6H_4$	H	158–159°	$C_{15}H_{20}ClNO_2$	63.93	63.79	7.15	7.27
CH_3	CH_3	CH_3	α-C_4H_3S	H	157–159°	$C_{12}H_{16}ClNOS$	55.91	55.76	6.26	6.34
—$(CH_2)_5$—		CH_3	C_6H_5	H	152–154°	$C_{17}H_{22}ClNO$	69.97	69.84	7.60	7.82

TABLE III

β-HYDROXYETHYLAMINES



R	R^1	R^2	R^3	R^4	R^5	Method	M.p.	Formula	—Carbon, %— Calcd.	Found	Hydrogen, % Calcd.	Found
CH_3	CH_3	H	H	H	H	[d]	84–86°	$C_7H_{14}ClNO$	51.37	51.15	8.62	8.44
CH_3	CH_3	CH_3	H	H	H	[d]	88–90°	$C_8H_{16}ClNO$	54.08	54.39	9.08	8.62
CH_3	CH_3	C_2H_5	H	H	H	[a]	124–126°	$C_9H_{18}ClNO$	56.38	56.23	9.46	9.43
CH_3	CH_3	CH_2=CH—CH_2	H	H	H	[a]	119–120°	$C_{10}H_{18}ClNO$	58.96	58.87	8.91	8.77
CH_3	CH_3	$(CH_3)_3C$	H	H	H	[a]	120–121°	$C_{11}H_{22}ClNO$	60.12	60.30	10.09	10.25
CH_3	CH_3	$HOCH_2CH_2$	H	H	H	[a]	82–84°	$C_9H_{18}ClNO_2$	52.04	52.18	8.74	8.85
CH_3	CH_3	C_6H_{11}	H	H	H	[a]	185–186°	$C_{13}H_{24}ClNO$	63.52	63.59	9.84	9.61
CH_3	CH_3	$C_6H_5CH_2CH_2$	H	H	H	[a]	168–169°	$C_{15}H_{22}ClNO$	67.27	67.27	8.28	8.48
CH_3	CH_3	p-CH_3—C_6H_4	H	H	H	[a]	105–107°	$C_{14}H_{20}ClNO$	66.26	65.98	7.94	7.84
CH_3	CH_3	m-ClC_6H_4	H	H	H	[a]	107–107.5°	$C_{13}H_{17}Cl_2NO$	[g]	[g]		
CH_3	CH_3	3Cl—4CH_3—C_6H_3	H	H	H	[a]	116–117°	$C_{14}H_{19}Cl_2NO$	58.34	58.58	6.64	6.56
CH_3	C_6H_5	C_2H_5	H	H	H	[a]	[e]	$C_{14}H_{19}NO$	77.38	77.33	8.81	8.77
$(CH_3)_2$-CH	$(CH_3)_2$-CH	H	H	H	H	[a]	113–116°	$C_{11}H_{22}ClNO$	60.12	59.90	10.09	10.24
—$(CH_2)_5$—		C_2H_5	H	H	H	[a]	147–149°	$C_{12}H_{22}ClNO$	62.19	62.44	9.57	9.46
CH_3	CH_3	C_2H_5	H	CH_3	H	[c]	148–150°	$C_{10}H_{20}ClNO$	58.38	58.43	9.80	9.75
CH_3	CH_3	CH_3	H	H	CH_3	[a]	78–82°	$C_9H_{18}ClNO$	56.38	56.37	9.46	9.54
CH_3	CH_3	C_2H_5	H	H	CH_3	[a]	166–168°	$C_{10}H_{20}ClNO$	58.38	58.34	9.80	9.54
CH_3	CH_3	CH_3	CH_2=CH	H	H	[a]	108–109°	$C_{10}H_{18}ClNO$	58.97	58.98	8.90	8.75
CH_3	CH_3	C_2H_5	$HOCH_2$	H	H	[a]	127–128°	$C_{10}H_{20}ClNO_2$	54.17	54.34	9.09	8.79
CH_3	CH_3	C_2H_5	$(CH_3)_2CHOCH_2$	H	H	[a]	108–109°	$C_{13}H_{26}ClNO_2$	59.18	59.01	9.94	10.26
CH_3	CH_3	C_2H_5	$C_6H_5OCH_2$	H	H	[a]	167–168°	$C_{18}H_{24}ClNO_2$	64.74	64.93	8.15	8.16
CH_3	CH_3	C_2H_5	CH_2=$CHCH_2OCH_2$	H	H	[a]	96–97°	$C_{13}H_{24}ClNO_2$	59.64	59.65	9.24	9.58
CH_3	CH_3	CH_3	$(C_2H_5)_2NCH_2$	H	H	[a]	195–196°	$C_{13}H_{29}Cl_2N_2O$	52.19	52.19	9.43	9.35
CH_3	CH_3	H	C_6H_5	H	H	[a]	135–137°	$C_{13}H_{18}ClNO$	65.12	64.95	7.57	7.73
CH_3	CH_3	CH_3	C_6H_5	H	H	[a,b]	129–131°	$C_{14}H_{20}ClNO$	66.26	66.29	7.94	7.81
CH_3	CH_3	C_2H_5	C_6H_5	H	H	[b]	158–160°	$C_{15}H_{22}ClNO$	67.27	67.63	8.28	8.03
CH_3	CH_3	C_2H_5	p-CH_3—C_6H_4	H	H	[b]	147–149°	$C_{16}H_{24}ClNO$	68.19	68.06	8.58	8.39
CH_3	CH_3	C_2H_5	p-$CH_3OC_6H_4$	H	H	[b]	138–140°	$C_{16}H_{24}ClNO_2$	64.52	64.42	8.12	7.97
CH_3	CH_3	C_2H_5	o-ClC_6H_4	H	H	[b]	163–165°	$C_{15}H_{21}Cl_2NO$	59.60	59.74	7.00	6.92
CH_3	CH_3	C_2H_5	p-ClC_6H_4	H	H	[b]	156–158°	$C_{15}H_{21}Cl_2NO$	59.60	59.89	7.00	7.06
CH_3	CH_3	CH_3	α-C_4H_3S	H	H	[b]	140–142°	$C_{12}H_{18}ClNOS$	55.47	55.75	6.98	7.18
CH_3	CH_3	p-$(CH_3)_2NC_6H_4$	CH_3	H	H	[a]	[f]	$C_{16}H_{24}N_2O$	73.80	73.70	9.29	9.25
CH_3	CH_3	CH_3	—$(CH_2)_3$—		H	[b]	173–175°	$C_{11}H_{20}ClNO$	60.67	60.52	9.26	9.10
CH_3	CH_3	H	—$(CH_2)_4$—		H	[a]	186–187°	$C_{11}H_{20}ClNO$	60.67	60.54	9.26	9.42

[a] Epoxide. [b] From ketone. [c] From ester. [d] β-Hydroxyethylamine with the 3-chloro-3-methyl-1-butyne. [e] Free base, b.p. 90° at 0.01 mm. [f] Free base, b.p. 148–154° at 5 mm. [g] N. Calcd.: 5.11; Found: 5.41.

and the ether removed. The residue was distilled giving 28 g. (26.5%) of crude ethyl N-ethyl-N-(1,1-dimethylpropargyl)-2-aminopropionate, b.p. 42–44°/0.1 mm., $n^{25}D$ 1.4458.

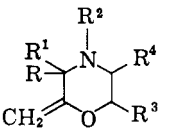
The crude ester, 28 g. (0.13 mole), was added dropwise to 500 ml. of ether containing 15.2 g. (0.4 mole) of lithium aluminum hydride, and the resulting mixture was stirred at 25° overnight. The excess lithium aluminum hydride was decomposed with dilute sodium hydroxide. The mixture was filtered; the ether solution was dried over magnesium sulfate, filtered, and concentrated at reduced pressure. The residue was distilled giving 11 g. (50%) of product, b.p. 70–73°/7 mm., $n^{25}D$ 1.4595. The hydrochloride was prepared and recrystallized from methyl ethyl ketone, m.p. 148–150°.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80. Found: C, 58.43; H, 9.75.

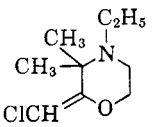
2-Methylenemorpholines (V) (Table IV).—To 200 ml. of vigorously refluxing toluene or xylene containing 5 g. of coarsely ground potassium hydroxide there was added dropwise 0.2 mole of the N-(2-hydroxyalkyl)propargylamine, and the resulting mixture was refluxed an additional 2 hr. The mixture was then cooled, filtered, and the solvent removed. The residue was distilled at reduced pressure. Yields of 75–85% were obtained.

TABLE IV

METHYLENE MORPHOLINES



R	R¹	R²	R³	R⁴	B.p.	Pressure, mm.	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	$n^{25}D$
CH_3	CH_3	CH_3	H	H	50°	5	$C_8H_{15}NO$	68.04	67.86	10.71	10.96	1.4663
CH_3	CH_3	C_2H_5	H	H	50°	5	$C_9H_{17}NO$	69.63	69.82	11.04	10.95	1.4653
CH_3	CH_3	CH_2=$CHCH_2$	H	H	56–57°	4	$C_{10}H_{17}NO$	71.81	71.60	10.25	10.23	1.4770
CH_3	CH_3	$C_6H_5CH_2CH_2$	H	H	85–86°	0.03	$C_{15}H_{21}NO$	77.88	77.71	9.15	8.99	1.5262
CH_3	CH_3	*p*-$CH_3C_6H_4$	H	H	84°	0.05	$C_{14}H_{19}NO$	77.38	77.12	8.81	8.53	1.5390
CH_3	CH_3	*o*-$CH_3OC_6H_4$	H	H	86–88°	0.1	$C_{14}H_{19}NO_2$	72.07	72.25	8.21	8.10	1.5460
CH_3	C_6H_5	C_2H_5	H	H	78–80°	0.03	$C_{14}H_{19}NO$	77.38	77.31	8.81	8.97	1.5327
—$(CH_2)_5$—		C_2H_5	H	H	60–62°	0.04	$C_{12}H_{21}NO$	73.79	73.65	10.84	11.03	1.4989
CH_3	CH_3	C_2H_5	H	CH_3	57°	5	$C_{10}H_{19}NO$	70.96	71.39	11.32	11.79	1.4644
CH_3	CH_3	C_2H_5	CH_3	H	55°	5	$C_{10}H_{19}NO$	70.96	70.72	11.32	11.02	1.4580
CH_3	CH_3	C_2H_5	$HOCH_2$	H	[a]		$C_{10}H_{19}NO_2$	64.83	64.92	10.34	10.07	
CH_3	CH_3	C_2H_5	$(CH_3)_2CHOCH_2$	H	55–56°	0.03	$C_{13}H_{25}NO_2$	68.68	68.94	11.08	11.02	1.4550
CH_3	CH_3	C_2H_5	CH_2=$CHCH_2OCH_2$	H	72°	0.05	$C_{13}H_{23}NO_2$	69.29	69.14	10.29	10.23	1.4700
CH_3	CH_3	C_2H_5	$(C_2H_5)_2NCH_2$	H	64–66°	0.1	$C_{14}H_{28}N_2O$	69.95	70.18	11.74	11.73	1.4671
CH_3	CH_3	CH_3	C_6H_5	H	95°	0.3	$C_{14}H_{19}NO$	77.38	77.08	8.81	8.69	1.5311
CH_3	CH_3	C_2H_5	C_6H_5	H	94–96°	0.1	$C_{15}H_{21}NO$	77.88	78.01	9.15	8.93	1.5252



88° 4 $C_9H_{16}ClNO$ 56.98 57.07 8.50 8.66 1.4912

[a] M.p. 99–101°.

2-Methylmorpholines (X) (Table V).—The 2-methylenemorpholine (0.1 mole) was hydrogenated in 100 ml. of ethanol under approximately 40 p.s.i.g. of hydrogen using 0.5 g. of 5% palladium on carbon as the catalyst. The catalyst was removed by filtration, and the filtrate was made acidic to Congo Red with anhydrous hydrogen chloride. The alcohol was distilled at reduced pressure; the residue was dissolved in water, made strongly basic with 50% sodium hydroxide solution, and extracted with ether. The ether solution was dried over magnesium sulfate, filtered, the ether was removed, and the residue was distilled at reduced pressure. A hydrochloride salt was prepared from the distillate and was recrystallized from methyl ethyl ketone or ethyl acetate. Yields of 80–90% were obtained.

2-Hydroxy-2-methylmorpholines (VI) (Table VI). Method A (from the N-(2-Hydroxyalkyl)propargylamine).—The N-(2-hydroxyalkyl)propargylamine (0.2 mole) was added dropwise to a mixture of 30 g. of sulfuric acid, 2 g. of red mercuric oxide, 30 ml. of methanol, and 30 ml. of water (the rate of addition was adjusted to maintain a gentle reflux). The reaction mixture was then refluxed an additional 4 hr., and 2 g. each of filter aid and powdered charcoal were added. The warm mixture was filtered with suction; the filtrate was cooled, treated with an excess of 50% sodium hydroxide solution, and extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and the ether removed. The residue was distilled at reduced pressure. A hydrochloride of the distillate was recrystallized from methyl ethyl ketone. Yields of 40–50% were obtained.

Method B (from the 2-Methylenemorpholines).—The 2-methylenemorpholine (0.1 mole) was dissolved in 200 ml. of 5% hydrochloric acid and allowed to stand at room temperature for 2 hr. The acidic solution was then treated with excess sodium hydroxide and extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and the ether removed. The residue was distilled at reduced pressure, and the hydrochloride from the distillate was recrystallized from methyl ethyl ketone. Yields of 40–50% were obtained.

Method C (from the β-Ketoamines and Ethylene Oxide).—The β-ketoamine (0.25 mole) and ethylene oxide (0.3 mole) were caused to react by the method described for Ia. The product was distilled and the hydrochloride crystallized from methyl ethyl ketone. Yields of 40–50% were obtained.

N-(2-Hydroxyethyl)-N-ethyl-2-methyl-3-hydroxy-2-butylamine (IX). Method A.—4-Ethyl-2-hydroxy-2,3,3-trimethylmorpholine, 17.3 g. (0.1 mole), was added dropwise to 500 ml. of ether containing 10 g. (0.3 mole) of lithium aluminum hydride, and the mixture was stirred for 4 hr. The excess hydride was decomposed with dilute sodium hydroxide, and the solids were removed by filtration. The ether solution was then dried over magnesium sulfate, filtered, and the ether removed. The residue was distilled at reduced pressure giving two fractions: first, b.p. 66–68°/10 mm. (structure undetermined), and second, b.p. 122–133°/10 mm., giving 10 g. (66%) of the desired product. A hydrochloride was prepared from a small sample of the distillate and recrystallized from acetone, m.p. 72–74°.

Anal. Calcd. for $C_9H_{22}ClNO_2$: C, 51.05; H, 10.47. Found: C, 51.25; H, 10.35.

Method B.—3-Methyl-3-ethylamino-2-butanol, 13 g. (0.1 mole), as prepared by the procedure given in ref. 3, and ethylene oxide, 5.3 g. (0.12 mole), were caused to react using method Ia. The product, 5 g. (35%), was in all respects identical to the product obtained by the preceding method A.

N-(2-Hydroxy-2-phenylethyl)-N-ethyl-2-methyl-3-hydroxy-2-butylamine.—N-Ethyl-2-hydroxy-2,3,3-trimethyl-6-phenylmorpholine, 28 g. (0.11 mole), was treated with 8.4 g. of lithium aluminum hydride by the method previously described, giving 14 g. (50%) of product boiling at 130–140°/0.05 mm. A hydrochloride was prepared from a small sample of the distillate and crystallized from a mixture of methyl ethyl ketone and isopropyl alcohol, m.p. 181–183°.

Anal. Calcd. for $C_{15}H_{26}ClNO$: C, 62.59; H, 9.11. Found: C, 62.51; H, 9.21.

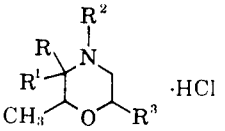
N-Ethyl-2,3,3-trimethylmorpholine (X).—To 75 ml. of 48% hydrobromic acid was added 3 g. (0.023 mole) of N-(2-hydroxyethyl)-N-ethyl-2-methyl-3-hydroxy-2-butylamine and the solution was refluxed 4 hr. The excess hydrobromic acid was removed at reduced pressure, the residue dissolved in water, made basic with sodium hydroxide, and the mixture extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and distilled b.p. 40°/5 mm., giving 1 g. (30%) of product. The hydrochloride from the distillate was prepared and was recrystallized from ethyl acetate, m.p. 192–194° (see Table V).

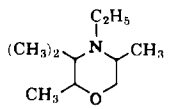
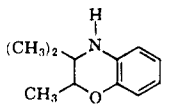
Anal. Calcd. for $C_9H_{20}ClNO$: C, 55.80; H, 10.41. Found: C, 55.82; H, 10.53.

N-Ethyl-2,3,3-trimethyl-6-phenylmorpholine.—A mixture of 10 g. of *p*-toluenesulfonic acid monohydrate and 10 g. of N-

TABLE V

MORPHOLINES

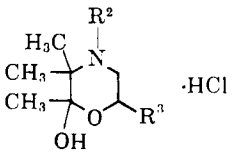


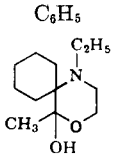
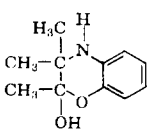
R	R¹	R²	R³	M.p.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	CH_3	H	H	159–161°	$C_7H_{16}ClNO$	50.75	50.31	9.74	9.78
CH_3	CH_3	CH_3	H	167–169°	$C_8H_{18}ClNO$	53.47	53.65	10.10	10.08
CH_3	CH_3	C_2H_5	H	191–193°	$C_9H_{20}ClNO$	55.80	55.54	10.41	10.12
CH_3	CH_3	$C_6H_5CH_2CH_2$	H	199–201°	$C_{15}H_{24}ClNO$	66.77	66.62	8.97	8.99
CH_3	CH_3	*p*-$CH_3C_6H_4$	H	154–156°	$C_{14}H_{22}ClNO$	65.74	65.94	8.67	8.76
CH_3	CH_3	*o*-$CH_3OC_6H_4$	H	183–185°	$C_{14}H_{22}ClNO_2$	62.87	62.95	8.16	7.95
CH_3	CH_3	4-CH_3-3-Cl-C_6H_3	H	[a]	$C_{12}H_{20}ClNO$	66.26	66.55	7.94	7.87
CH_3	C_6H_5	C_2H_5	H	[b]	$C_{14}H_{21}NO$	76.66	76.51	9.65	9.71
—$(CH_2)_5$—		C_2H_5	H	168–170°	$C_{12}H_{24}ClNO$	61.65	61.99	10.35	10.35
CH_3	CH_3	C_2H_5	CH_3	122–124°	$C_{10}H_{22}ClNO$	57.81	58.06	10.67	10.69
CH_3	CH_3	C_2H_5	$CH_3CH_2CH_2OCH_2$[c]	132–134°	$C_{13}H_{28}ClNO_2$	58.74	59.03	10.62	10.73
CH_3	CH_3	C_2H_5	$(CH_3)_2CHOCH_2$	106–108°	$C_{13}H_{28}ClNO_2$	58.74	58.87	10.62	10.67
CH_3	CH_3	H	C_6H_5	243–246° (dec.)	$C_{13}H_{20}ClNO$	64.58	64.59	8.34	8.18
CH_3	CH_3	CH_3	C_6H_5	181–183°	$C_{14}H_{22}ClNO$	65.74	65.70	8.62	8.92
CH_3	CH_3	C_2H_5	C_6H_5	194–196°	$C_{15}H_{24}ClNO$	66.77	67.11	8.97	9.24
CH_3	CH_3	C_2H_5	*p*-$CH_3C_6H_4$	180–182°	$C_{16}H_{26}ClNO$	67.70	67.54	9.23	9.05
CH_3	CH_3	C_2H_5	*p*-$CH_3OC_6H_4$	165–167°	$C_{16}H_{26}ClNO_2$	64.09	63.87	8.74	8.68
CH_3	CH_3	C_2H_5	*p*-ClC_6H_4	164–166°	$C_{15}H_{23}Cl_2NO$	59.21	59.17	7.62	7.89
				180–182°	$C_{10}H_{22}ClNO$	57.81	57.55	10.67	10.51
				190–192°	$C_{11}H_{16}ClNO$	61.82	61.60	7.55	7.77

[a] Free base, b.p. 100–102° at 0.08 mm. [b] Free base, b.p. 86° at 0.03 mm. [c] Prepared by the catalytic reduction of 2-methylene-3,3-dimethyl-4-ethyl-6-allyloxymethylmorpholine.

TABLE VI

2-HYDROXYMORPHOLINES



R²	R³	M.p.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	H	155–157°	$C_8H_{18}ClNO_2$	49.10	49.06	9.27	9.13
C_2H_5	H	173–177°	$C_9H_{20}ClNO_2$	51.54	51.46	9.61	9.66
$HOCH_2CH_2$	H	105–106°[a]	$C_9H_{19}NO_3$	57.11	56.91	10.12	10.04
o-$CH_3OC_6H_4$	H	144–146°	$C_{14}H_{22}ClNO_3$	58.43	58.63	7.71	7.43
4-CH_3—3-Cl—C_6H_3	H	[b]	$C_{14}H_{19}ClNO$	[c]			
C_2H_5	CH_3	182–184°	$C_{10}H_{22}ClNO_2$	53.68	53.91	9.91	10.03
C_2H_5	$C_6H_5OCH_2$	169–170°	$C_{16}H_{25}ClNO_3$	60.84	61.15	8.30	8.63
C_2H_5	C_6H_5	153–155°	$C_{15}H_{24}ClNO_2$	63.03	63.38	8.46	8.51
		148–150°	$C_{12}H_{24}ClNO_2$	57.70	57.82	9.69	9.64
		174–176°	$C_{11}H_{16}ClNO_2$	57.51	57.58	7.02	7.38

[a] Free base. [b] Free base, b.p. 110° at 0.08 mm. [c] N. Calcd.: 5.19. Found: 5.07.

(2 - hydroxy - 2 - phenylethyl) - N - ethyl - 2 - methyl - 3 - hydroxy-2-butylamine hydrochloride in 250 ml. of xylene was refluxed overnight. After cooling, the mixture was washed with water. The aqueous layer was separated, treated with excess 50% sodium hydroxide solution, and extracted with ether. The organic layer was dried over magnesium sulfate, filtered, and the solvent removed at reduced pressure. The residue boiled at 90–92°/0.3 mm. The hydrochloride of the distillate was recrystallized from ethyl acetate, m.p. 193–195°.

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97. Found: C, 66.96; H, 8.82.

3-(2-Chloroethoxy)-3-methyl-1-butyne (XI).—The 3-chloro-3-methyl-1-butyne, 102.5 g. (1.0 mole), was added dropwise to 500 g. of ethylene glycol containing 60 g. of sodium hydroxide. The mixture was stirred for 2 days after which 500 ml. of water was added, and the mixture extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and the ether was removed from the filtrate at reduced pressure. The residue was distilled, giving 28 g. (22%) of crude 3-(2-hydroxyethxoxy)-3-methyl-1-butyne, b.p. 80–85°/20 mm.

A solution of the crude distillate (0.22 mole) and 71 g. (0.6 mole) of thionyl chloride in 250 ml. of benzene was stirred overnight. The benzene and excess thionyl chloride were removed at reduced pressure and the residue distilled, giving 23 g. (70%) of product, b.p. 56–60°/20 mm.

Anal. Calcd. for $C_7H_{11}ClO$: C, 57.34; H, 7.57. Found: C, 57.18; H, 7.39.

3-(2-Ethylaminoethoxy)-3-methyl-1-butyne (XII).—A mixture of 23 g. (0.157 mole) of 3-(2-chloroethoxy)-3-methyl-1-butyne and 52 g. (0.8 mole) of 70% ethylamine was refluxed for 36 hr. (An additional 25 g. of 10% ethylamine was added after 12 hr.). The cooled mixture was then treated with 15 g. of 10% sodium hydroxide solution and extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and the ether removed. The residue was distilled at reduced pressure giving 10 g. (46%) of product, b.p. 88°/30 mm., $n^{25}D$ 1.4372. The hydrochloride, prepared from a small amount of the distillate, was recrystallized from methyl ethyl ketone, m.p. 76–78°.

Anal. Calcd. for $C_9H_{18}ClNO$: C, 56.38; H, 9.46. Found: C, 56.15; H, 9.43.

2,2,3-Trimethyl-4-ethylmorpholine (XIV).—The 3-(2-ethylaminoethoxy)-3-methyl-1-butyne, 10 g. (0.065 mole), was added dropwise to a mixture of 10 g. of sulfuric acid, 1 g. of red mercuric oxide, 12 ml. of methanol, and 12 ml. of water. (The rate of addition was adjusted to maintain a gentle reflux.) After refluxing for an additional 3 hr., 1 g. of filter aid and 1 g. of powdered charcoal were added, and the warm mixture was filtered with suction. The cooled filtrate was made strongly basic with sodium hydroxide, and extracted with ether. The ether solution was dried over magnesium sulfate and filtered. The filtrate was distilled at reduced pressure and the product collected at 54°/7 mm., giving 3 g. (30%) of a clear oil. The distillate was hydrogenated in 50 ml. of ethanol using 0.1 g. of 5% palladium on carbon as catalyst at approximately 40 p.s.i.g. of hydrogen. The catalyst was removed by filtration, and anhydrous hydrogen chloride was added to the filtrate until the solution was acidic to congo red. The ethanol was removed at reduced pressure and the residue crystallized from ethyl acetate, m.p. 195–197°, giving 3 g. (24%) of product.

Anal. Calcd. for $C_9H_{20}ClNO$: C, 55.50; H, 10.41. Found: C, 55.53; H, 10.58.

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Phenylhydrazide as a Protective Group in Peptide Synthesis. The Oxidation of γ-Phenylhydrazides of N-Carbobenzoxy-α-L-glutamylamino Acid Esters with Manganese Dioxide

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The synthesis of some γ-phenylhydrazides of N-carbobenzoxy-α-L-glutamylamino acid esters (III) is described. Treatment of aqueous acetic acid solutions of these compounds with manganese dioxide, at room temperature, results in the rapid oxidation of the phenylhydrazide group to a carboxylic acid leaving the carbobenzoxy group and the ester intact and without racemization. The use of the phenylhydrazide group as a protective group in peptide synthesis is suggested.

An an extension of our synthetic work in the agaritine series,[1] we have synthesized some γ-phenylhydrazides of N-carbobenzoxy-α-L-glutamylamino acid esters (III). These were obtained in good yield by condensing either N-carbobenzoxy-L-glutamic acid γ-phenylhydrazide[1] (Ia) or N-carbobenzoxy-L-glutamic acid γ-(*p*-tolylhydrazide)[1] (Ib) with amino acid esters using N-ethyl-5-phenylisoxazolium-3′-sulfonate[2] as condensing agent. Compounds of type III which have been synthesized to date along with the yields in which they were obtained are listed in Table I.

Aside from their novelty, dipeptides of type III are of interest because of their mode of oxidation with manganese dioxide. When aqueous acetic acid solutions were treated with activated manganese dioxide[3] at room temperature, the phenylhydrazide group was rapidly oxidized to a carboxylic acid,[4] with the evolution of gas, leaving the protecting carbobenzoxy and ester groups intact. A period of thirty to forty minutes is adequate for complete oxidation. The yields of the acid were good, in some cases excellent; a summary of the results obtained is given in Table II.

(1) R. B. Kelly, E. G. Daniels, and J. W. Hinman, *J. Org. Chem.*, **27**, 3229 (1962).

(2) Woodward's reagent, K. R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961); R. B. Woodward, R. A. Olofson, and H. Mayer, *ibid.*, **83**, 1010 (1961).

(3) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(4) *Cf.* H. B. Milne, J. E. Halver, D. S. Ho, and M. S. Mason, *J. Am. Chem. Soc.*, **79**, 637 (1957); E. Waldschmidt-Leitz and K. Kühn, *Ber.*, **84**, 381 (1951).