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Acetylenic 1,4-Aminoalcohols[1]

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Twenty new acetylenic 1,4-aminoalcohols have been prepared by the condensation of acetylenic amines, $R^1R^2C(NR^3R^4)$-C≡CH, with carbonyl compounds. Yields ranged from 2 to 90%, depending on the nature of the carbonyl reagent and condensing agent employed. Assorted derivatives were prepared by hydrogenation, acylation, etc.

DISCUSSION

A recent paper[3] in this series described the condensation of 3-amino-3-methyl-1-pentyne with a few carbonyl compounds. It is evident that the reaction involved namely,

$$R^1R^2C(NR^3R^4)C\equiv CH + R^5COR^6 \rightarrow R^1R^2C(NR^3R^4)—C\equiv C—C(OH)R^5R^6$$

may be used to prepare a very large number of new compounds. Since some of these may well have useful drug properties, it was considered worth while to study the reaction in some detail and to make available a good assortment of the aminoalcohols for broad screening.[4]

The methods used to effect the desired reaction are illustrated in Tables I and II. It will be seen that yields varied widely and depend on the nature of the carbonyl reagent and the particular condensing agent employed.

TABLE I

2-AMINO-2-METHYL-5-PHENYL-3-HEXYNE-5-OL (VI) FROM CONDENSATION OF 3-AMINO-3-METHYL-1-BUTYNE WITH ACETOPHENONE

Method	Condensing agent (moles)	Moles of Ketone	Yield, %
A	$LiNH_2$-NH_3 (0.22)	0.20	7
B	$LiNH_2$-ether (0.21)	.20	trace
C	C_2H_5MgBr-ether (0.21)	.20	11
C	C_2H_5MgBr-ether (0.40)	.20	12
D	$NaNH_2$-NH_3 (0.62)	.60	2
E	KNH_2-NH_3 (0.32)	.30	trace

The step-wise hydrogenation of several of the acetylenic aminoalcohols was studied. It appears that reduction by sodium in liquid ammonia and hydrogenation with 5% Pd-$BaCO_3$ produces the *trans*- and *cis*-olefinic analogs, respectively, while hydrogenation with Raney nickel affords the saturated derivatives.

TABLE II

3-AMINO-3,6-DIMETHYL-4-OCTYNE-6-OL (XIV) FROM CONDENSATION OF 3-AMINO-3-METHYL-1-PENTYNE WITH METHYL ETHYL KETONE

Method	Condensing agent (moles)	Moles of Ketone	Yield, %
A	$LiNH_2$-NH_3 (0.23)	0.20	52
B	$LiNH_2$-ether (0.21)	.20	4
C	C_2H_5MgBr-ether (0.20)	.20	7
C	C_2H_5MgBr-ether (0.40)	.23	6
D	$NaNH_2$-NH_3 (0.40)	.30	35
E	KNH_2-NH_3 (0.23)	.20	36

The acetylenic aminoalcohols were readily transformed to the N-benzoyl and N-acetyl derivatives, which, unlike the aminoalcohols, are not soluble in dilute acid. Further evidence for the expected N-acylation was obtained in the case of 1-(9′-hydroxy-9′-fluorenyl)-3-methyl-3-amino-1-pentyne (XIII) where the benzoyl derivative was oxidized to N-benzoyl-isovaline and fluorenone.

The carbon disulfide reaction with the acetylenic aminoalcohols having the —NH_2 group yielded thiazolidine-2-thione derivatives as previously reported.[3]

The new acetylenic aminoalcohols are described in Tables III and IV.

EXPERIMENTAL

Acetylenic amines. 3-Amino-3-methyl-1-butyne, 3-amino-3-methyl-1-pentyne, 3-ethylamino-3-methyl-1-pentyne, and 3-amino-1-hexyne were prepared as previously described.[3,5]

3-Chloro-1-butyne was prepared from 1-butyn-3-ol[6] by treatment with thionyl chloride.[7] From 70 g. (1 mole) of carbinol, 130 g. of thionyl chloride, and 1.5 g. of pyridine, the yield of chloride was 50 g. (57%), b.p. 68–69°, n_D^{25} 1.4221. A redistilled portion had b.p. 68.5°, n_D^{25} 1.4218, d^{25} 0.9466.

Anal. Calc'd for C_4H_5Cl: Cl, 40.05. Found: Cl, 39.70.

3-Amino-1-butyne. Sodium (23 g.) was converted to sodamide in 900 ml. of liquid ammonia and 70 g. of 3-

(1) Paper LXII on substituted acetylenes; previous paper, *J. Am. Chem. Soc.*, **77**, 3253 (1955).

(2) Eli Lilly and Co. Fellow, 1952–1955. Abstracted from the Ph.D. Dissertation of J. M. C., Univ. of Notre Dame, 1955.

(3) G. F. Hennion and E. G. Teach, *J. Am Chem. Soc.*, **75**, 4297 (1953). *Cf.* H. Huggill and J. Rose, *J. Chem. Soc.*, 335 (1950).

(4) Pharmacological testing is in progress in the Lilly Research Laboratories, Indianapolis, Indiana.

(5) G. F. Hennion and E. G. Teach, *J. Am. Chem. Soc.*, **75**, 1653 (1953).

(6) G. F. Hennion and W. S. Murray, *J. Am. Chem. Soc.*, **64**, 1220 (1942); R. Lespieau, *Bull. soc. chim.*, **39**, 991 (1926).

(7) G. F. Hennion and J. J. Sheehan, *J. Am. Chem. Soc.*, **71**, 1964 (1949).

TABLE III

ACETYLENIC 1,4-AMINOALCOHOLS, $R^1R^2C(NR^3R^4)—C{\equiv}C—C(OH)R^5R^6$, FROM CONDENSATION OF ACETYLENIC AMINES WITH CARBONYL COMPOUNDS

Compd.	Carbonyl Compd.	Product	Method
	A. FROM 3-AMINO-1-BUTYNE		
I	Benzophenone	1,1-Diphenyl-4-amino-2-pentyne-1-ol	A
	B. FROM 3-AMINO-3-METHYL-1-BUTYNE		
II	Methyl ethyl ketone	2-Amino-2,5-dimethyl-3-heptyne-5-ol	D
III	Acetone	2,5-Dimethyl-5-amino-3-hexyne-2-ol	D
IV	Benzophenone	1,1-Diphenyl-4-amino-4-methyl-2-pentyne-1-ol	D
V	Methyl *n*-amyl ketone	2-Amino-2,5-dimethyl-3-decyne-5-ol	D
VI	Acetophenone	2-Amino-2-methyl-5-phenyl-3-hexyne-5-ol	Table I
VII	Diisopropyl ketone	2-Amino-2,6-dimethyl-5-isopropyl-3-heptyne-5-ol	D
VIII	3-Methylcyclohexanone	1-(1-Hydroxy-3-methylcyclohexyl)-3-amino-3-methyl-1-butyne	A
	C. FROM 3-DIMETHYLAMINO-3-METHYL-1-BUTYNE		
IX	Benzophenone	1,1-Diphenyl-4-dimethylamino-4-methyl-2-pentyne-1-ol	A
	D. FROM 3-AMINO-3-METHYL-1-PENTYNE		
X	Cyclohexanone	1-(1-Hydroxycyclohexyl)-3-amino-3-methyl-1-pentyne	D
XI	3-Methylcyclohexanone	1-(1-Hydroxy-3-methylcyclohexyl)-3-amino-3-methyl-1-pentyne	A
XII	Veratraldehyde	1-(3,4-Dimethoxyphenyl)-4-amino-4-methyl-2-hexyne-1-ol	C
XIII	Fluorenone	1-(9-Hydroxy-9-fluorenyl)-3-amino-3-methyl-1-pentyne	D
XIV	Methyl ethyl ketone	3-Amino-3,6-dimethyl-4-octyne-6-ol	Table II
XV	Methyl *n*-propyl ketone	3-Amino-3,6-dimethyl-4-nonyne-6-ol	A
XVI	Methyl *n*-heptadecyl ketone	3-Amino-3,6-dimethyl-4-tricosyne-6-ol	A
XVII	Benzaldehyde	1-Phenyl-4-amino-4-methyl-2-hexyne-1-ol	B
	E. FROM 3-ETHYLAMINO-3-METHYL-1-PENTYNE		
XVIII	Acetone	2,5-Dimethyl-5-ethylamino-3-heptyne-2-ol	D
XIX	Fluorenone	1-(9-Hydroxy-9-fluorenyl)-3-ethylamino-3-methyl-1-pentyne	D
	F. FROM 3-AMINO-1-HEXYNE		
XX	Benzophenone	1,1-Diphenyl-4-amino-2-heptyne-1-ol	D

TABLE IV

MELTING POINTS, YIELDS, AND ANALYSES, ACETYLENIC 1,4-AMINOALCOHOLS

Compd.	Mol. Formula	Yield, %	M.p., °C.[a]	Nitrogen Calc'd	Nitrogen Obs'd
I	$C_{17}H_{17}NO$	41	116.5–117.5	5.57	5.63
II	$C_9H_{17}NO$	68	60–62.5	9.02	9.22
III	$C_8H_{15}NO$	13	79–80	9.92	10.03
IV	$C_{18}H_{19}NO$	6	130–131	5.28	5.00
V	$C_{12}H_{23}NO$	17	32–34	7.10	7.10
VI	$C_{18}H_{17}NO$	Table I	62–64	6.89	6.82
VII	$C_{12}H_{23}NO$	26	47–49	7.10	6.88
VIII	$C_{12}H_{21}NO$	15	74.5–76	7.17	7.09
IX	$C_{20}H_{23}NO$	30	155.5–157	4.78	4.68
X	$C_{12}H_{21}NO$	38	70.5–71	7.17	7.00
XI	$C_{13}H_{23}NO$	21	63–66	6.69	6.48
XII	$C_{15}H_{21}NO_3$	48	oil	5.32	5.75
XIII	$C_{19}H_{19}NO$	85	151–152.5	5.05	4.74
XIV	$C_{10}H_{19}NO$	Table II	51–53	8.28	8.34
XV	$C_{11}H_{21}NO$	36	41–42	7.64	7.68
XVI	$C_{25}H_{49}NO$	26	59.5–61	3.69	3.72
XVII	$C_{13}H_{17}NO$	32	60–61.5	6.89	6.96
XVIII	$C_{11}H_{21}NO$	7	75–77	7.65	7.79
XIX	$C_{21}H_{23}NO$	87	166–167.5	4.59	4.50
XX	$C_{19}H_{21}NO$	89	95–96	5.01	5.19

[a] Uncorrected.

chloro-1-butyne in 260 ml. of anhydrous ether was added dropwise with stirring. The product was isolated in the usual way.[5] Two distillations yielded 18.7 g. of amine, b.p. 82–83.5°, n_D^{25} 1.4305, d^{25} 0.812.

The amine (2 g.) was converted to the hydrochloride in anhydrous ether, and the precipitate was crystallized from a mixture of ethyl acetate and absolute ethanol; m.p. 166–167° (sealed cap., dec.); yield, 1.6 g.

Anal. Calc'd for C_4H_8ClN: N, 13.27. Found: N, 13.13.

3-Dimethylamino-3-methyl-1-butyne. To a cold solution of 83 g. (1 mole) of 3-amino-3-methyl-1-butyne[6] in 100 ml. of ether was added 252 g. (2 moles) of dimethyl sulfate in 200 ml. of ether with stirring (45 minutes). The solution then was refluxed with stirring for 1 hour, cooled by means of an ice-bath, and 164 g. (4.1 moles) of sodium hydroxide in 250 ml. of water was added with stirring (30 minutes). The mixture was refluxed again for 2 hours and 100 ml. of water and 100 ml. of ether then were added. The ethereal layer was separated and the aqueous layer was extracted three times with 100-ml. portions of ether. The combined ethereal solution was dried with potassium carbonate and the ether was removed by distillation, leaving a white, crystalline residue of 3-dimethylamino-3-methyl-1-butyne, wt. 32 g. This material proved difficult to purify because of its extreme volatility. Sublimation gave 30 g. of product, m.p. sealed cap., 100.5–102° (lit.[6] 97–98°).

(8) I. G. Farbenindustrie, French Patent 839,875 (1939); *Chem. Abstr.*, **33**, 7820 (1939).

The *hydrochloride*, precipitated from ether and crystallized from a mixture of ethyl acetate and absolute ethanol, had m.p. 234–236.5° (uncorr., sealed cap., with dec.).

Anal. Calc'd for $C_7H_{14}ClN$: N, 9.49. Found: N, 9.46.

Acetylenic 1,4-aminoalcohols were prepared from the acetylenic amines by condensation with carbonyl compounds according to the methods illustrated below. All melting points are uncorrected.

3-Amino-3,6-dimethyl-4-octyne-6-ol (XIV). *Method A.* Lithium (1.6 g., 0.23 g.-atom) was converted to the amide in 500 ml. of liquid ammonia and 19.4 g. (0.2 mole) of 3-amino-3-methyl-1-pentyne dissolved in 50 ml. of anhydrous ether was added dropwise with stirring. After 15 minutes 14.4 g. (0.2 mole) of methyl ethyl ketone diluted with 50 ml. of ether was added dropwise with stirring (15 minutes). The stirring was continued for 4 hours and the mixture was allowed to stand overnight. Methanol (10 ml.), 200 g. of chopped ice, and 50 ml. of ether were added, and the ethereal layer was separated and the aqueous layer was extracted with 50 ml. of ether. The combined ethereal layers were dried superficially with magnesium sulfate and then with potassium carbonate. The ether was removed by distillation (last portion *in vacuo*) and the waxy residue was crystallized from petroleum ether; yield 17.6 g. (52%), m.p. 50–51°. Recrystallization raised the m.p. to 51–53°.

Method D. The procedure described above was repeated using sodium in place of lithium; yield, 35%.

Method E. Use of potassium in place of lithium gave a 36% yield.

Method B. Lithium (1.46 g., 0.21 g.-atom) was converted to the amide in 300 ml. of liquid ammonia and 20.4 g. (0.21 mole) of 3-amino-3-methyl-1-pentyne in 100 ml. of anhydrous ether was added dropwise with stirring. More ether was added (*ca.* 100 ml.) and the ammonia was removed by heating with cold water and finally with the aid of a stream of dry nitrogen while heating to reflux temperature. Methyl ethyl ketone (14.4 g., 0.2 mole) diluted with 150 ml. of anhydrous ether was added dropwise with stirring. The product was recovered essentially as described above; yield 1 g. (3%), m.p. 51–52°.

4-Methyl-4-ethyl-5-(2'-methyl-2'-hydroxybutylidene)thiazolidine-2-thione. The aminoalcohol (XIV) described above (5 g.) was treated with 5 ml. of carbon disulfide in 30 ml. of absolute ethanol as previously reported.[3] Crystallization from a mixture of ethyl alcohol and cyclohexane gave 5.1 g. of product, m.p. 145–146°.

Anal. Calc'd for $C_{11}H_{19}NOS_2$: N, 5.71. Found: N, 5.44.

2-Amino-2-methyl-5-phenyl-3-hexyne-5-ol (VI). *Method C.* Ethylmagnesium bromide was prepared from 5.1 g. of magnesium turnings, 22 g. of ethyl bromide, and 100 ml. of anhydrous ether. 3-Amino-3-methyl-1-butyne (16.6 g., 0.2 mole) in 100 ml. of anhydrous ether was added dropwise with stirring (40 minutes). The pasty mass so formed was diluted with 50 ml. of ether and refluxed for 40 minutes. Acetophenone (24.0 g., 0.2 mole) in 100 ml. of ether was added dropwise (20 minutes) and the mixture was refluxed with stirring for 2 hours. Hydrolysis was effected with saturated ammonium chloride solution, and the ether layer was separated and sufficient 10% hydrochloric acid was added to extract the basic material (*p*H 1–2 in the aqueous layer). The ether layer was extracted once with 100 ml. of 10% HCl and the combined acidic aqueous extract was made alkaline with 30% potassium hydroxide solution. The alkaline aqueous solution then was extracted with two 75-ml. portions of ether. The ethereal solution was dried with magnesium sulfate and then with potassium carbonate, filtered, and the ether was removed by distillation (finally *in vacuo*). The residue solidified slowly and the product was purified by crystallization from a mixture of benzene and petroleum ether; yield 5.6 g. (11%), m.p. 62.5–64°.

4,4-Dimethyl-5-(2'-phenyl-2'-hydroxypropylidene)thiazolidine-2-thione. The aminoalcohol (VI) described above (5 g.) with 5 ml. of carbon disulfide in 40 ml. of ethanol gave 4.4 g. of product after one crystallization from ethyl alcohol. After two recrystallizations the m.p. was 145–146°.

Anal. Calc'd for $C_{14}H_{17}NOS_2$: N, 5.01. Found: N, 4.82.

trans-1,1-Diphenyl-4-amino-4-methyl-2-hexene-1-ol. One-tenth mole (27.9 g.) of 1,1-diphenyl-4-amino-4-methyl-2-hexyne-1-ol (m.p. 108–109°; hemisulfate, m.p. 198°) described in an earlier paper[3] was added to 5.8 g. (0.25 g.-atom) of sodium in 1 liter of liquid ammonia with 530 ml. of ether. The mixture was stirred for several hours and 13.4 g. (0.25 mole) of ammonium chloride was added in small portions. The product was allowed to stand overnight, 15 ml. of methanol was added to wash down the sides of the flask, and 100 g. of chopped ice was added. The ethereal layer was separated and the aqueous layer was extracted with 100 ml. of ether. The combined ether extract was dried with magnesium sulfate, filtered, and the ether was removed by distillation. The residue was cooled with ice, a small amount of petroleum ether was added, and the solution was scratched to induce crystallization. The product was collected and recrystallized from a mixture of petroleum ether and benzene; yield 12.2 g. (43%); m.p. 91.5–92° after an additional recrystallization. The *hemisulfate* had m.p. 185–187° (dec.).

Anal. Calc'd for $C_{19}H_{23}NO$: N, 4.98. Found: N, 4.93.

cis-1,1-Diphenyl-4-amino-4-methyl-2-hexene-1-ol. Hydrogenation of 17.5 g. of 1,1-diphenyl-4-amino-4-methyl-2-hexyne-1-ol with 0.555 g. of 5% Pd-$BaCO_3$ in 175 ml. of 95% ethyl alcohol at an initial pressure of 61 p.s.i.g. gave 9.5 g. of product after one crystallization from petroleum ether; m.p. 79–80.5°. Recrystallization raised the m.p. to 80–81.5°. (The saturated product,[3] obtained by hydrogenation with Raney nickel, melts at 94–95°.)

Anal. Calc'd for $C_{19}H_{23}NO$: N, 4.98. Found: N, 4.89.

1,1-Diphenyl-4-acetylamino-2-heptyne-1-ol. 1,1-Diphenyl-4-amino-2-heptyne-1-ol (XX), m.p. 95–96° (5 g.), was heated with 10 ml. of acetic anhydride for 5 minutes, cooled, and the product was collected by filtration, washed well with water, and crystallized from aqueous ethanol. Yield, 4.4 g., m.p. 171–172°. Recrystallization gave large crystals, m.p. 173–174°.

Anal. Calc'd for $C_{21}H_{23}NO_2$: N, 4.36. Found: N, 4.45.

1-(9'-Hydroxy-9'-fluorenyl)-3-benzoylamino-3-methyl-1-pentyne. A mixture of 20 ml. of 5% sodium hydroxide solution, 50 ml. of chloroform, 7 g. of benzoyl chloride, and 9.2 g. of 1-(9'-hydroxy-9'-fluorenyl)-3-amino-3-methyl-1-pentyne (XIII) was shaken frequently over a period of 24 hours. The chloroform layer was separated and the aqueous layer was extracted with 20 ml. of chloroform. The combined chloroform solution was washed three times with 20-ml. portions of water, dried with potassium carbonate, filtered, and concentrated to a volume of about 30 ml. The solution was cooled and 100 ml. of cyclohexane was added. The precipitate was crystallized from a mixture of petroleum ether and benzene; yield, 9.5 g., m.p. 162.5–163.5°, not altered by recrystallization.

Anal. Calc'd for $C_{26}H_{23}NO_2$: N, 3.67. Found: N, 3.60.

Oxidation. A suspension of 6 g. of the benzoylamino derivative described above in 100 ml. of 0.3% KOH solution was heated to 60–80° and treated with 6.6 g. of potassium permanganate, added in small portions, over 4.5 hours. The mixture was stirred for an additional 7 hours at about 70°, filtered, and the filtrate was made strongly acid with conc'd HCl. The solution was concentrated somewhat and cooled to crystallize the N-benzoyl-*dl*-isovaline; yield 2 g. After crystallization from aqueous alcohol the m.p. was 195° (sealed cap., uncorr., with dec.); N.E. Calc'd, 221, N.E. Obs'd, 219. (Lit.[9] m.p. 198–199°.) The manganese dioxide cake recovered from the oxidation was subjected to

(9) M. D. Slimmer, *Ber.*, **35**, 407 (1902).

continuous ether extraction for 7 hours, the ether was distilled, and the residue was crystallized from aqueous alcohol. Yield of fluorenone 1.8 g., m.p. 82–83.5°, raised to 83–84° by recrystallization and not depressed by an authentic sample.

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