A mixture of the product from Methods A and B melted at 185–186°.

t-Butyl-3,4-dimethylpentylamine. A solution of the Schiff's base V (prepared in a similar manner to III) in ethanol was hydrogenated over Raney nickel under 40 p.s.i. of hydrogen. After filtration the solution was made acidic with alcoholic hydrogen chloride and concentrated at reduced pressure. The residue was crystallized from methyl ethyl ketone. The solid which separated was largely *t*-butylamine hydrochloride. The mother liquors were concentrated, and the solid was recrystallized twice from ethyl acetate, m.p. 177–179°.

Anal. Calcd. for $C_{11}H_{25}NCl$: C, 63.89; H, 12.19; N, 6.77. Found: C, 63.80; H, 12.16; N, 6.42.

α-Acetylenic amines by the dimethylformamide method. 3-Isopropylamino-3,4-dimethyl-1-pentyne. To a mixture of 280 g. (4.65 moles) of isopropylamine, 2 g. of cuprous chloride, 2 g. of copper bronze, and 1 l. of dimethylformamide, there was added, dropwise with stirring, 180 g. (1.38 moles) of 3,4-dimethyl-3-chloropentyne. The mixture was stirred overnight at room temperature, and 1 l. of water was added followed by 1.5 moles of 50% sodium hydroxide. The solution was extracted with ether, and the ether layer was washed with water, dried over magnesium sulfate, and concentrated at reduced pressure. The residue was distilled under vacuum, and the product collected at 45–47°/6 mm. weighed 70 g. (33%), n_D^{25} 1.4315.

Preparation of saturated amines. In addition to the method previously published,[4] the following procedure was used: an alcoholic solution of the amine and two equivalents of hydrogen chloride was hydrogenated over platinum oxide at 40 p.s.i. of hydrogen. The catalyst was filtered and the solution was concentrated at reduced pressure. The hydrochloride was purified by recrystallization or converted to the free base which could be purified by distillation (see Table IV).

Acknowledgment. The authors wish to thank Dr. George Hennion for his many helpful suggestions in the various phases of this work. The analyses were performed by Messrs. William L. Brown, Howard L. Hunter, George Maciak, Ralph Hughes, and Miss Gloria Beckmann. Some of the hydrogenations were carried out by Mr. William B. Scanlon. Mr. Donald O. Woolf, Jr., and Miss Martha Hofmann provided the infrared data.

INDIANAPOLIS, IND.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Highly Hindered Aliphatic Tertiary Amines

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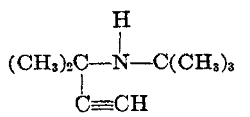
The preparation of a progression of highly hindered aliphatic noncyclic tertiary amines by alkyl sulfate treatment of hindered secondary amines is reported. The yield of tertiary amines is decreased with increased steric hindrance of the nitrogen, and the limitation by steric hindrance is shown. *N*-(*t*-Amyl)-*N*-(*t*-butyl)methylamine has the unusually high pK_a of 11.9 when determined in water.

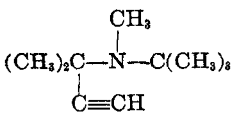
N-(*t*-Amyl)-*N*-(isopropyl)methylamines form quaternary methyl iodides that are stable at room temperature, but *N*-(*t*-amyl)-*N*-(*t*-butyl)methylamines do not and decomposition products are isolated.

During the past decade, hindered tertiary amines were investigated, among others, by Brown[1] and by Hall,[2] who determined the basic strength of a number of representative compounds. Pharmacologically, it was discovered that certain hindered tertiary amines were effective ganglionic blocking agents.[3] The methods described by Hennion[4] were applied in this laboratory to obtain a series of hindered acetylenic secondary amines[5] of the type



$$(CH_3)_2C(C{\equiv}CH)-N(H)-C(CH_3)_3$$

I



$$(CH_3)_2C(C{\equiv}CH)-N(CH_3)-C(CH_3)_3$$

II

represented by compound I. Certain of these compounds displayed considerable pharmacological effect, and therefore, the corresponding tertiary compounds—*e.g.*, II—were desired. This paper reports a study of the problem of converting such secondary amines to highly hindered tertiary amines and quaternization studies of the latter.

3-*t*-Butylamino-3-methyl-1-butyne (I) was treated in various ways to study its conversion to the corresponding tertiary amines. The Eschweiler-Clarke method employing formaldehyde–formic acid proved to be sensitive to the amount of formic acid and the time of heating. Excess of formic acid at reflux temperature was accompanied with loss of isobutylene and formation of 3-dimethylamino-3-methyl-1-butyne. However, by running the reaction for a longer period of time at a lower temperature, 3-[*N*-(*t*-butyl)methylamino]-3-methyl-1-butyne (II) was obtained in good yield.[6] This tertiary amine, like others later described, was characterized by a higher refractive index (about 0.02 unit) than the corresponding secondary amine. In addition, *the picrates of the tertiary amines were all found to be relatively insoluble in ethanol,* whereas the picrates of the starting secondary amines were soluble in ethanol. This fact proved helpful in

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(1) H. C. Brown and R. B. Johannesen, *J. Am. Chem. Soc.*, **75**, 16 (1953).

(2) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5444 (1957).

(3) H. Spinks and E. H. P. Young, *Nature*, **181**, 1397 (1958).

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

(5) N. R. Easton *et al.*, *J. Org. Chem.*, **26**, 3772 (1961).

(6) This method was developed by Wm. L. Garbrecht.

the separation of the mixtures of these amines. Finally, the constitution of the tertiary amines was verified by the absence of the NH_2^+ band at 6.28 μ in the infrared absorption pattern that is characteristic of the secondary amine hydrochloride salts of this series.

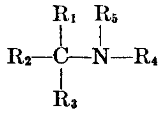
Initial studies of the reaction of I with methyl *p*-toluenesulfonate showed II formed in low yield only. As 3 - isopropylamino - 3 - methyl - 1 - pentyne and ethyl *p*-toluenesulfonate gave a small amount of the corresponding tertiary amine, this method was not further investigated.

The use of alkyl halides as agents for the alkylation of the secondary amines proved to have limitations. It was found that I, methyl iodide and potassium carbonate in ethyl alcohol or acetone at room temperature for four days gave II in 20% yield. When the mixture was heated decomposition took place, and the quaternary salt, 3-dimethylamino-3-methyl-1-butyne methiodide, was also isolated. When pure dimethylformamide was used as solvent, a small amount of insoluble product formed that proved to be tetramethylammonium iodide.[7] The method failed when higher alkyl halides such as ethyl iodide, propyl iodide, or benzyl chloride were used, with ethanol as solvent, at room temperature for one week.

The method most employed for the preparation of tertiary amines of this series was the use of equimolar quantities of dialkyl sulfate, potassium carbonate, and secondary amine. The mixture was heated with stirring, in the absence of a solvent, and usually an exothermic reaction took place when the temperature reached 100°. The amines contained in Table I were prepared by this method. It appears that the yield of tertiary amine is decreased with increased steric hindrance of the nitrogen. It was found that when R_4 was *t*-butyl (compounds II and III), methylation occurred when R_1=R_2=methyl but did not occur when either of the groups was larger than methyl. This finding also applied when the degree of unsaturation of the two carbon fragment R_3 was varied. However, the tertiary amines (compounds VII–X) were formed when R_4 was isopropyl and the R_1 and R_2 groups were larger than methyl.

The tertiary amines listed in Table I, for convenience of handling and identification, were converted in good yield to the hydrochloride salts. The physical properties of these hydrochlorides are given in Table II. Each of the compounds was examined by infrared analysis and displayed expected characteristic features. It was noted that when the hydrochloride of compound III was heated, it decomposed at 135°, emitting an odorless gas. A new solid formed that melted at 185°, and this material was shown to be 3-ethylamino-

TABLE I. TERTIARY AMINES



$$R_2-\overset{R_1}{\underset{R_3}{C}}-\overset{R_5}{N}-R_4$$

Compound	R_1	R_2	R_3	R_4	R_5	B.P. °C	B.P. Mm.	Yield, %	n_D^{25}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
II	CH_3	CH_3	C≡CH	X[a]	CH_3	110–112°	130	25	1.4510	$C_{10}H_{19}N$	78.36	78.17	12.50	12.32	9.14	9.21
III	CH_3	CH_3	C≡CH	X	C_2H_5	110–120°	130	7	1.4440	$C_{11}H_{21}N$[b]						
IV	CH_3	CH_3	CH=CH_2	X	CH_3	80–85°	55	10	1.4385	$C_{10}H_{21}N$[b]						
V	CH_3	CH_3	CH_2—CH_3	X	CH_3	100–110°	120	28	1.4370	$C_{10}H_{23}N$[b]						
VI	CH_3	CH_3	C≡CH	Y[c]	CH_3	96–98°	135	65	1.4350	$C_9H_{17}N$	77.63	77.25	12.31	12.62	10.06	9.93
VII	CH_3	$CH(CH_3)_2$	C≡CH	Y	CH_3	73–75°	20	60	1.4450	$C_{11}H_{21}N$	78.97	79.32	12.65	12.89	8.37	8 47
VIII	C_2H_5	C_2H_5	C≡CH	Y	CH_3	72–74°	14	60	1.4465	$C_{11}H_{21}N$	78.97	78.48	12.65	12.00	8.37	8.69
IX	C_2H_5	C_2H_5	C≡CH	Y	C_2H_5	93–95°	25	20	1.4485	$C_{12}H_{23}N$	79.49	79.75	12.79	12.56	7.73	8.02
X	CH_3	C_2H_5	CH=CH_2	Y	CH_3	100–101°	90	50	1.4410	$C_{10}H_{21}N$	77.35	76.99	13.63	13.52	9.02	9.37
XI[d]	CH_3	CH_3	CH_2—CH_3	Y	CH_3	90–91°	110	10	1.4260	$C_9H_{21}N$					9.78	9.52

[a] X is *tert.*butyl. [b] Analyzed as the picrate salt. III·picrate, m.p. 130° dec. *Anal.* Calcd. for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.10; N, 14.14. Found: C, 51.62; H, 6.21; N, 14.11. IV·picrate m.p. 142° dec. *Anal.* Calcd. for $C_{16}H_{24}N_4O_7$: C, 49.99; H, 6.29; N, 14.58. Found: C, 49.96; H, 6.22; N, 14.45. (The analytical sample was dried under reduced pressure at room temperature for 6 hr.) V·picrate, m.p. 148° dec. *Anal.* Calcd. for $C_{26}H_{26}N_4O_7$: C, 49.73; H, 6.78; N, 14.50. Found: C, 49.89; H, 6.54; N, 14.59. [c] Y is isopropyl. [d] Prepared by catalytic reduction of VI using Raney nickel and ethanol. The low yield is attributed to hydrogenolysis.

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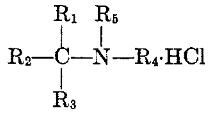
[7] N. Kornblum and R. K. Blackwood, *J. Am. Chem. Soc.*, 78, 4037 (1956), studied the reaction of alkyl halides and dimethylformamide but did not observe the formation of this product.

TABLE II

Tertiary Amine Hydrochlorides



$$R_2\text{—}\overset{\overset{R_1}{|}}{\underset{\underset{R_3}{|}}{C}}\text{—}\overset{\overset{R_5}{|}}{N}\text{—}R_4\cdot HCl$$

Compound[a]	M.P.	Recrystallization Solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Titration, pK_a DMF[b]	H_2O[c]
II·HCl	138–140[d]	[e]	$C_{10}H_{19}N\cdot HCl$					7.38	7.35	7.9	9.3
III.HCl	135 dec.	[f]	$C_{11}H_{21}N\cdot HCl$	64.84	64.56	10.88	10.83	6.88	7.00	8.0	9.6
IV·HCl	127 dec.	[f]	$C_{10}H_{21}N\cdot HCl$		[g]			7.31	7.72	9.6	11.3
V·HCl	107–108	[h]	$C_{10}H_{23}N\cdot HCl$	61.98	62.35	12.49	12.60	7.23	7.23	10.6	11.9[i]
VI·HCl	185–186[d]	[e]	$C_9H_{17}N\cdot HCl$	61.52	61.80	10.33	10.07	7.97	8.13	7.5	8.7
VII·HCl	198 dec.	[f]	$C_{11}H_{21}N\cdot HCl$	64.84	65.09	10.88	11.05	6.88	6.80	6.8	8.7
VIII·HCl	143–145	[f]	$C_{11}H_{21}N\cdot HCl$	64.84	64.67	10.88	10.97	6.88	7.09	7.1	8.8
IX·HCl	165–167	[f]	$C_{12}H_{23}N\cdot HCl$	66.18	66.00	11.11	10.93	6.43	6.20	6.8	8.2
X·HCl	90–91	[j]	$C_{10}H_{21}N\cdot HCl$		[g]			7.31	7.06	9.3	11.3
XI·HCl	142–144[d]	[k]	$C_9H_{21}N\cdot HCl$	60.14	60.08	12.34	11.82	7.79	7.82	9.9	11.2

[a] Roman numbers correspond to those of Table I. [b] Titration values determined at 25° in 66% dimethylformamide. [c] The pK data below 11.0 are accurate. The values above 11.0 for experimental reasons have an error of approximately ±0.2 pK units. [d] Capillary. [e] Isopropyl alcohol–ethyl acetate. [f] Ethanol-ether. [g] The compound exploded on analysis destroying the combustion tube [h] Acetone-ether, after digestion with ethyl acetate. [i] Verified by ultraviolet absorption technique. [j] Benzenemethylcyclohexane on long standing. [k] Methyl ethyl ketone.

3-methyl-1-butyne hydrochloride. The gas evolved was identified as isobutylene.[8]

The pK_a data of the tertiary amines are given in Table II. Hall[2,9] has noted that the base strength of tertiary amines increases with increased steric effects, and has presented evidence that this is a polar effect. The number of related amines contained in Table II is insufficient to permit any general conclusions, but it is of note that compound V has such an unusually high pK_a value.

Quaternization of the hindered tertiary amines was investigated. Compound II and methyl iodide at room temperature formed 3-dimethylamino-3-methyl-1-butyne methiodide. Presumably, isobutylene was split out at some stage of the alkylation Compounds VII, VIII, IX, and X behaves similarly on standing with methyl iodide and formed mixtures of tertiary amine hydroiodides and quaternary products that were not separated. Compounds VI and XI formed stable quaternary compounds when treated with methyl iodide.

The pharmacological findings will be reported elsewhere.

EXPERIMENTAL[10]

General procedure. One-tenth mole each of the secondary amine,[4,5] dimethyl sulfate, and potassium carbonate was placed in a round bottom flask, equipped with a stirrer, and the mixture was heated by means of a heating mantle. As the temperature approached 90–100°, exothermic reaction usually ensued, and the flask was cooled with a water bath. Following the initial temperature rise, the mixture was heated (compound number, temperature, and time of heating in hours: II, 100, 3; III, 100, 12; IV, 65, 3; V, 60, 4; VI, VII, VIII, IX, 110, 2; X, 100, 1.5; XI, 100, 2). About 50 ml. of water was added, and the mixture was poured into 120 ml. of cold 3*N* hydrochloric acid contained in a relatively large beaker. The acidic solution was extracted with ether, and the aqueous layer was made strongly basic with 10 g. of sodium hydroxide. The ether extract of the basic solution was washed with a small volume of water and dried with anhydrous magnesium sulfate. The ether was evaporated, and the remaining oil was distilled. The free bases II, VI–XI contained in Table I were prepared in this manner.

When the alkylation procedure was applied to the *t*-butyl amines, the yield of tertiary amines was low and separation by fractional distillation was difficult. It was found that the tertiary bases formed picrates that were readily recrystallized from 95% ethyl alcohol, whereas the secondary amine picrates were soluble. Compounds III, IV, and V were isolated as picrate salts.

The hydrochlorides described in Table II were prepared in high yield by adding hydrogen chloride contained in ether to an ethereal solution of the tertiary amine.

The picrate salts were converted to the hydrochloride salts by extracting a nitrobenzene solution of the picrate salt with concentrated hydrochloric acid. The acidic extract was washed with chloroform and then was evaporated under reduced pressure to yield the hydrochloride.

3-t-Butylamino-3-methyl-1-butyne and formaldehyde–formic acid (a) A mixture of 52.5 g. (0.37 mole) of 3-*t*-butylamino-3-methyl-1-butyne, 75 ml. of formalin, and 27.6 g. (0.6 mole) of 100% formic acid was heated under reflux for 2 hr. After cooling, the solution was made basic with 50% sodium hydroxide and was extracted with ether. The ethereal solution was dried with anhydrous magnesium sulfate, and then the ether was removed by heating on a steam bath. The resulting oil was distilled under reduced pressure to yield 32 g. (55%) of 3-[*N*-(*t*-butyl)methylamino]-3-methyl-1-butyne (II), b.p. 108–110° (130 mm.), n_D^{25} 1.4500.

(b) A solution of 33 g. of 3-*t*-butylamino-3-methyl-1-butyne, 75 ml. of formalin, and 75 ml. of formic acid was heated under reflux overnight and isobutylene was evolved. When treated according to the above procedure, the product

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[8] This type of elimination reaction will be the subject of a separate communication.

[9] H. K. Hall, Jr., *J. Am. Chem. Soc.*, 79, 5441 (1957).

[10] The melting points, unless otherwise indicated, were determined with a Fisher-Johns assembly and are reported as read.

obtained from the reaction was 3-dimethylamino-3-methylbutyne.[11]

(c)[6] A mixture of 60 g. (1.5 mole) of 98% formic acid, 6 ml. of water and 45 g. (1.5 mole) of paraformaldehyde was warmed to 60° and 139 g. (1 mole) of 3-*t*-butylamino-3-methyl-1-butyne was added slowly so the temperature was maintained at 60–65°. After heating near 60° for 20 hr. the reaction mixture was cooled, made basic with 50% sodium hydroxide and the product was extracted with ether. The ether was removed by heating on a steam bath and the residue was distilled under reduced pressure to give compound II in 80% yield.

3-Isopropylamino-3-methyl-1-pentyne and ethyl p-toluenesulfonate. A mixture of 37 g. (0.26 mole) of 3-isopropylamino-3-methyl-1-pentyne and 60 g. (0.30 mole) of ethyl *p*-toluenesulfonate was heated on a steam bath for 1 day. About 30 g. of dry powdered potassium carbonate was added and heating was continued for 3 hr. After cooling, 100 ml. of 3*N* sodium hydroxide was added and the mixture was extracted with ether. The ethereal solution was dried with anhydrous magnesium sulfate, and the ether was removed by heating on a steam bath. The resulting oil was distilled at atmospheric pressure to remove any material boiling below 138°. The residue was dissolved in ether and was treated with hydrogen chloride dissolved in dry ether. The resulting salt was recrystallized from methyl ethyl ketone and weighed 2.9 g. (7% yield). 3-[*N*-Ethylisopropylamino]-3-methyl-1-pentyne hydrochloride melted at 177–179°, pK_a 7.45 (66% dimethylformamide).

Anal. Calcd. for $C_{11}H_{21}N\cdot HCl$: N, 6.88. Found: N, 7.3.

3-*t*-Butylamino-3-methyl-1-butyne (I) and methyl *p*-toluenesulfonate gave a small yield of II.

3-t-Butylamino-3-methyl-1-butyne and methyl iodide. (a) A mixture of 6.5 g. (0.05 mole) of 3-*t*-butylamino-3-methyl-1-butyne,[4] 12 g. (0.1 mole) of anhydrous potassium carbonate, 13 g. (0.1 mole) of methyl iodide, and 50 ml. of ethanol was placed in a stoppered flask and allowed to stand at room temperature for 4 days. About 50 ml. of water was added and the solution was poured into 100 ml. of 3*N* hydrochloric acid contained in a relatively large beaker. The solution was concentrated to dryness by heating under reduced pressure. The residue was dissolved in 50 ml. of 6*N* sodium hydroxide and was extracted with 100 ml. of chloroform. The chloroform solution was heated on a steam bath[12] to remove the solvent, and the residue was treated with 50 ml. of saturated 95% ethanol solution of picric acid. The picrate salt that separated was recrystallized from 95% ethanol and gave 4 g. (20% yield) of 3-[*N*-(*t*-butyl)methylamino]-3-methyl-1-butyne picrate, m.p. 155° dec.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.43; H, 5.88; N, 14.66.

The picrate was converted to II·HCl according to the method described in the general procedure.

(b) The reactants described in procedure (a) were heated under reflux on a steam bath overnight. About 300 ml. of ether was added, and after cooling, the salts were collected by filtration. The filtrate was distilled and the tertiary amine (II) was obtained in 10% yield. The filter cake was extracted with hot ethanol, and this extract on cooling gave 3-dimethylamino-3-methyl-1-butyne methiodide, identical with the material prepared from 3-dimethylamino-3-methyl-1-butyne and methyl iodide dissolved in acetone, m.p. 210° dec.

Anal. Calcd. for $C_8H_{16}IN$: C, 37.96; H, 6.37; N, 5.53. Found: C, 38.11; H, 6.51; N, 5.56.

(c) A solution of 6.5 g. (0.05 mole) of 3-*t*-butylamino-3-methyl-1-butyne and 13 g. (0.1 mole) of methyl iodide dissolved in 50 ml. of dimethylformamide was allowed to stand at room temperature for 4 days. The solid (0.5 g.) that separated was collected by filtration and was shown to be tetramethylammonium iodide. The filtrate was treated according to the directions of procedure (a), and a small yield of II·picrate, m.p. 155° dec., was obtained.

Quaternization experiments. (a) *3-[N-(Isopropyl)methylamino]-3-methyl-1-butyne and methyl iodide.* A solution of 1.39 g. (0.01 mole) of VI and 1.4 g. (0.01 mole) of methyl iodide was allowed to stand in a stoppered flask at room temperature for 2 days. The solid that formed was recrystallized from ethanol-ether and gave 0.28 g. (10% yield) of 3 - (*N* - (isopropyl)methylamino) - 3 - methyl - 1 - butyne methiodide, m.p. 157–158° dec.

Anal. Calcd. for $C_{10}H_{20}IN$: C, 42.71; H, 7.17; N, 4.98. Found: C, 42.92; H, 7.10; N, 5.12.

No titratable group was observed between the *p*H range 3.5–14. The infrared absorption pattern was consistent with the structure, showing acetylenic CH at 3.04 μ.

When compounds VII, VIII, IX, and X were substituted for VI in the above reaction, some decomposition took place, and the solids that formed were shown by infrared analysis to be mixtures of tertiary amine hydroiodides and quaternary compounds.

(b) *3-N[-(Isopropyl)methylamino]-3-methylbutane and methyl iodide.* A mixture of 4.3 g. (0.03 mole) of XI and 4.3 g. (0.03 mole) of methyl iodide was allowed to stand in a closed vessel at room temperature for 4 weeks. The white solid that separated was washed with ether and was recrystallized from ethanol–ethyl acetate–ether mixture to give 2 g. (23% yield) of 3-[*N*-(isopropyl)methylamino]-3-methylbutane methiodide, m.p. 147–148°.

Anal. Calcd. for $C_{10}H_{24}IN$: C, 42.11; H, 8.48; N, 4.91. Found: C, 42.35; H, 8.07; N, 4.93.

(c) *3-[N-(t-Butyl)methylamino]-3-methyl-1-butyne and methyl iodide.* A solution of 4.6 g. (0.03 mole) of II, 4.3 g. (0.03 mole) of methyl iodide, and 100 ml. of diethyl ether was allowed to stand in a stoppered flask at room temperature for 2 weeks. The solid that formed was recrystallized from ethanol and was shown by infrared analysis to be 3-dimethylamino-3-methyl-1-butyne methiodide, m.p. 210° dec.

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[11] G. F. Hennion and J. M. Campbell, *J. Org. Chem.*, **21**, 761 (1956).

[12] The amines of this type are volatile so prolonged heating must be avoided.