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Quaternary Salts from the Alkylation of Tertiary Amines with *t*-Propargylic Chlorides[1]

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Recently we reported[3] that *t*-propargylic chlorides, $R^1R^2C(Cl)-C\equiv CH$, alkylate trimethylamine to produce either propargylic or allenic quaternary salts depending on the size of R^1 and R^2, allenic products being produced when both are larger than CH_3. Further study of this reaction, employing a wide variety of tertiary amines as well as assorted *t*-propargylic chlorides, has revealed that it may take three courses which are shown in Scheme I. The particular

SCHEME I

$$R^1R^2C(Cl)-C\equiv CH + R^3R^4R^5N \longrightarrow \begin{cases} R^3R^4R^5N\cdot HCl + \text{enyne} \\ R^1R^2C(\overset{+}{N}R^3R^4R^5)-C\equiv CH(Cl^-) \\ R^1R^2C=C=CH-NR^3R^4R^5(Cl^-) \end{cases}$$

outcome in any one case depends not only on steric factors but also on the basicity and nucleophilicity of the particular tertiary amine employed. Quaternary salts, propargylic and/or allenic, appear to be the favored products from amines $R^3R^4NCH_3$ having pK_b in the range *ca.* 3.5–7.5. While weaker bases react very slowly, if at all, and stronger ones seemingly favor elimination, other factors certainly are involved.

Although it is not possible at this stage to disentangle and assess the solvation, basicity, nucleophilicity, and steric factors which favor quaternary salt formation over elimination, or determine whether the product will be propargylic or allenic, the following observations must be significant. The three reactions pictured above always proceed competitively; in most instances one, sometimes two, reactions are favored. Triethylamine, cyclohexyldimethylamine, dodecyldimethylamine, and 3-dimethylamino-3-methyl-1-butyne reacted chiefly by elimination and thus produced their own hydrochlorides as the only isolable products. Methyldiethylamine gave viscous oils which could not be crystallized; infrared examination indicated that the oils were mixtures of amine hydrochloride and both quaternary salts. N-methylpyrrolidine gave the propargylic quaternaries by reaction with 3-chloro-3-methyl-1-butyne and with 1-ethynylcyclohexyl chloride, but an oil, mostly the hydrochloride, by treatment with 3-chloro-3-ethyl-1-pentyne. N-methylpiperidine gave allenic quaternaries except again with 3-chloro-3-ethyl-1-pentyne which produced an oily mixture of hydrochloride and both quaternaries.

Dimethylpropyl-, dimethylallyl-, and dimethylpropargylamine, differing but little in steric features but significantly in basicity, gave good yields of quaternaries. Dimethylpropargylamine, the least basic of these three, uniquely produced the allenic and propargylic salts in about equal amounts, readily separated by selective extraction and recrystallization (see Experimental Section).

While no crystalline products were isolated from the treatment of pyridine with *t*-propargyl chlorides, the reaction of 2,4,6-collidine with 3-chloro-3-methyl-1-butyne gave a 35% yield of a brown salt, mp 203–204°, for which C,H,N analysis and infrared examination indicated a propargylic structure.

Propargylic and allenic quaternary ammonium salts [20 new] are described in Table I. It should be noted that all are hygroscopic and melt with decomposition; each one is a methochloride and hence was prepared from an amine $CH_3NR^3R^4$. Structures were established by infrared and pmr examination as previously reported.[3]

The pmr spectrum of 3-(N-propargylmethylamino)-3-methyl-1-butyne methochloride (Table I, compound II) showed a singlet at τ 5.4 assigned to methylene protons of the propargyl group, a singlet at τ 6.5 for the N-methyl protons, and a singlet at τ 7.9 for the C-methyl protons. The allenic isomer (Table I, compound XIV) showed a multiplet at τ 3.4 (allenic proton), a singlet at τ 5.6 assigned to the methylene protons of the propargyl group, a singlet at τ 6.7 (N-methyl protons), and a doublet with J = 2 cps at τ 8.1 assigned to the remaining methyl protons (both spectra in D_2O with water as internal standard).

Finally it should be stated that the various reaction products are believed to arise *via* zwitterion carbenes ($R^1R^2{}^+C-C\equiv C^- \longleftrightarrow R^1R^2C=C=C:$) as previously discussed.[3]

Experimental Section

Infrared spectra were obtained for chloroform solutions; pmr spectra with chloroform-*d* solutions with TMS as the internal standard or with D_2O solutions having water as the internal standard.

The *t*-propargylic chlorides were prepared as previously described.[4] Tertiary amines were purchased or prepared by methods given in the literature.

Quaternary chlorides were prepared by the procedure described earlier[3] except that the reactions were allowed to proceed for 24–72 hr depending on the rate of crystallization of product. In most instances the product was recovered by filtration; in some experiments the solvent (usually acetone) was removed by evaporation or distillation *in vacuo*. Crystallization usually was achieved using acetone, acetonitrile, ethyl acetate, absolute ethanol, chloroform, or an appropriate binary mixture of these.

Reaction of N,N-Dimethylpropargylamine with 3-Chloro-3-methyl-1-butyne.—A 0.1-mole scale experiment gave 11 g (60% yield) of crude product after 72 hr. Approximately half of this material dissolved by boiling with a mixture of acetonitrile and chloroform. Several crystallizations of the material so extracted (same solvent mixture) gave 1-(N-propargylmethylamino)-3-methyl-1,2-butadiene methochloride (XIV), mp 119–120°. The residue from the original extraction was crystallized from a mixture of ethyl acetate and isopropyl alcohol to give 3-(N-propargylmethylamino)3-methyl-1-butyne methochloride

(1) Paper no. 84 on substituted acetylenes. Previous paper: G. F. Hennion and R. H. Ode, *J. Org. Chem.*, **31**, 1975 (1966).

(2) Eli Lilly Co. Fellow, 1962–1965.

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TABLE I

QUATERNARY AMMONIUM SALTS

Compd	R^1	R^2	R^3	R^4	Yield, %[a]	Mol formula	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
					Propargylic, $R^1R^2C(\overset{+}{N}R^3R^4CH_3)C{\equiv}CH$ (Cl^-)								
I	CH_3	CH_3	CH_3	C_2H_5	53	$C_9H_{18}NCl$	181–183	61.52	61.52	10.32	10.42	7.97	7.77
II	CH_3	CH_3	CH_3	$CH_2C{\equiv}CH$	30[b]	$C_{10}H_{16}NCl$	177–178	64.68	64.97	8.69	8.93	7.54	7.48
III[c]	CH_3	CH_3	CH_3	$CH_2CH{=}CH_2$	56	$C_{10}H_{18}NCl$	142–145	62.00	62.15	9.71	9.66	7.23	7.21
IV	CH_3	CH_3	CH_3	$CH_2CH_2CH_3$	84	$C_{10}H_{20}NCl$	199–201	63.30	63.21	10.63	10.70	7.38	7.35
V	CH_3	CH_3	$-(CH_2)_4-$		67	$C_{10}H_{18}NCl$	182–183	63.98	63.76	9.66	9.80	7.46	7.24
VI	CH_3	CH_3	CH_3	CH_2CH_2OH	82	$C_9H_{18}NOCl$	168–170	56.39	55.89	9.46	9.70	7.31	7.19
VII	CH_3	CH_3	CH_3	$CH_2CH_2OCOCH_3$	65	$C_{11}H_{20}NO_2Cl$	166–167	56.52	56.27	8.63	8.80	5.99	6.00
VIII	$-(CH_2)_5-$		CH_3	C_2H_5	48	$C_{12}H_{22}NCl$	214–215	66.79	66.86	10.28	10.42	6.49	5.94
IX	$-(CH_2)_5-$		CH_3	$CH_2CH{=}CH_2$	43	$C_{13}H_{22}NCl$	194–195	68.55	68.83	9.73	9.83	6.15	6.03
X	$-(CH_2)_5-$		CH_3	$CH_2CH_2CH_3$	61	$C_{13}H_{24}NCl$	210–211	67.95	68.05	10.53	10.69	6.10	6.27
XI[d]	$-(CH_2)_5-$		CH_3	$CH_2C_6H_5$	32[b]	$C_{17}H_{24}NCl$	175–176	71.85	71.83	9.05	8.98	4.66	4.50
XII	$-(CH_2)_5-$		$-(CH_2)_4-$		57	$C_{13}H_{22}NCl$	197–198	68.55	68.96	9.74	9.98	6.15	5.82
XIII	$-(CH_2)_5-$		CH_3	CH_2CH_2OH	61	$C_{12}H_{22}NOCl$	181–182	62.18	62.30	9.57	9.63	6.04	6.09
					Allenic, $R^1R^2C{=}C{=}CH{-}\overset{+}{N}(NR^3R^4CH_3)(Cl^-)$								
XIV[e]	CH_3	CH_3	CH_3	$CH_2C{\equiv}CH$	30[b]	$C_{10}H_{16}NCl$	119–120	63.14	63.06	8.75	8.79	7.36	7.16
XV	CH_3	CH_3	$-(CH_2)_5-$		90	$C_{11}H_{20}NCl$	151–153	65.49	64.76	9.99	10.32	6.94	6.36
XVI	CH_3	C_2H_5	CH_3	$CH_2C_6H_5$	58	$C_{16}H_{22}NCl$	146–148	71.55	71.65	8.81	9.09	5.56	5.44
XVII	C_2H_5	C_2H_5	CH_3	$CH_2C_6H_5$	52	$C_{16}H_{24}NCl$	112–114	72.29	72.40	9.10	9.22	5.27	5.18
XVIII	$-(CH_2)_5-$		CH_3	$CH_2C{\equiv}CH$	50	$C_{13}H_{20}NCl$	133–135	69.16	69.02	8.93	8.99	6.20	5.94
XIX	$-(CH_2)_5-$		CH_3	$CH_2C_6H_5$	32[b]	$C_{17}H_{24}NCl$	149–151	73.49	73.39	8.71	8.82	5.04	4.84
XX	$-(CH_2)_5-$		$-(CH_2)_5-$		55	$C_{14}H_{24}NCl$	144–147	69.54	69.18	10.01	10.34	5.79	5.52

[a] Yield of crude material. [b] 50% of total product. [c] Analysis for $C_{10}H_{18}NCl \cdot {}^1/_3H_2O$. [d] Analysis for $C_{10}H_{16}NCl \cdot {}^1/_4H_2O$. [e] Analysis for $C_{17}H_{24}NCl \cdot {}^1/_2C_2H_5OH$.

(II), mp 177–178°. The pmr spectrum of each product and of the original crude material indicated that the latter contained the two products in nearly equal amounts.

3-(N-Methyl-β-acetoxyethylamino)-3-methyl-1-butyne methochloride (VII) was prepared by esterification of the hydroxy compound (VI) by heating with acetic anhydride (steam bath, 1 hr). The product, crystallized from acetonitrile, had mp 166–167° dec and showed infrared bands at 5.7 μ (ester carbonyl) and at 3.0 and 4.7 μ (ethynyl group).

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Characterization of an Intermediate in the Dithionite Reduction of a Diphosphopyridine Nucleotide Model as a 1,4-Addition Product by Nuclear Magnetic Resonance Spectroscopy[1]

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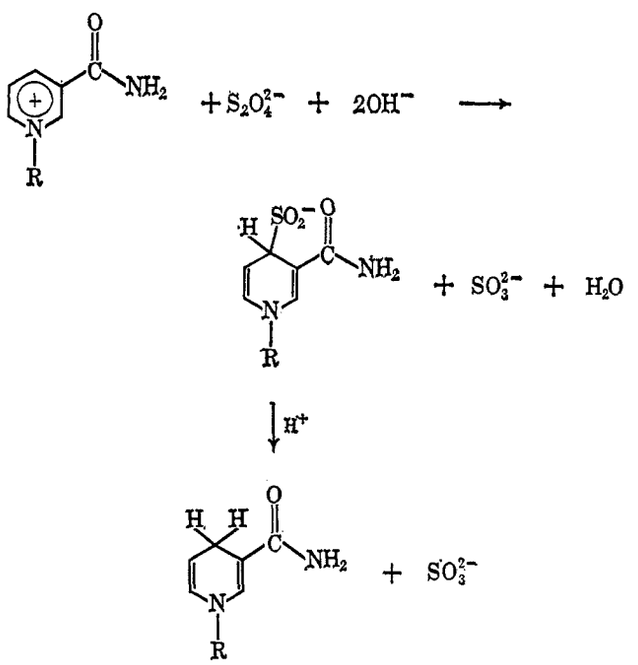
The yellow intermediate formed during the reduction of diphosphopyridine nucleotide (DPN) or its analogs was shown by Yarmolinsky and Colowick to decompose readily into the fully reduced compound ($DPNH_2$) and sulfite.[4] The reduction could thus be represented

SCHEME I



as shown in Scheme I. Here R could be adenosyldiphosphoribosyl, benzyl, or methyl. The yellow complex was studied only in solution where it was labile to air and neutralization, being stable only in strongly alkaline solution. Mauzerall and Westheimer[5] subsequently demonstrated the absence of paramagnetism associated with the intermediate.

The intermediate obtained from DPN exhibits a broad absorption band with λ_{max} at 357 mμ (ϵ 3200).[4] This absorption band is broader than that of other addition products of DPN. Unlike the labile alkali, cyanide, or acetone complexes,[6] the dithionite complex is not fluorescent.[4] Kosower and Bauer suggested that

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