[Contribution from the Department of Chemistry, University of Buffalo]

THE REACTION OF CYANOGEN WITH ORGANIC COMPOUNDS. III. SUBSTITUTION AND EXCHANGE REACTIONS OF DIALKYLOXAMIDINES[1, 2]

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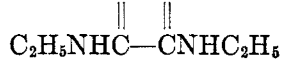
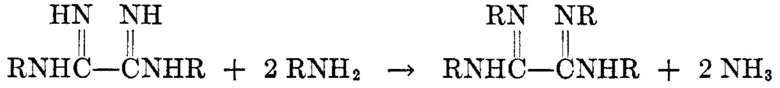
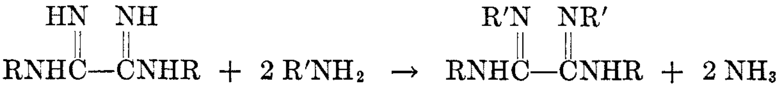
During our investigation of the behavior of primary aliphatic amines with cyanogen (1) we isolated several times from the ethylamine reaction mixture a product whose analysis, molecular weight, and chemical properties pointed to the structure  $C_2H_5NH\overset{\overset{C_2H_5N}{\|}}{C}-\overset{\overset{NC_2H_5}{\|}}{C}NHC_2H_5$ instead of to the expected disubstituted oxamidine. Although we have as yet been unable to discover conditions under which this compound can be obtained without fail directly from ethylamine and cyanogen, its isolation proved that tetrasubstituted oxamidines can exist and led us to study the possibility of converting disubstituted oxamidines into tetrasubstituted compounds by reaction with aliphatic amines.

Two aspects of the problem were investigated, first the possible formation of symmetrical tetrasubstituted oxamidines by the interaction of compounds containing the same alkyl group throughout,



$$\mathrm{RNH}\overset{\overset{\mathrm{HN}}{\|}}{\mathrm{C}}-\overset{\overset{\mathrm{NH}}{\|}}{\mathrm{C}}\mathrm{NHR} + 2\,\mathrm{RNH_2} \rightarrow \mathrm{RNH}\overset{\overset{\mathrm{RN}}{\|}}{\mathrm{C}}-\overset{\overset{\mathrm{NR}}{\|}}{\mathrm{C}}\mathrm{NHR} + 2\,\mathrm{NH_3}$$

and second, the possible formation of mixed substitution products by the use of an amine containing an alkyl group different from that present in the oxamidine.



$$\mathrm{RNH}\overset{\overset{\mathrm{HN}}{\|}}{\mathrm{C}}-\overset{\overset{\mathrm{NH}}{\|}}{\mathrm{C}}\mathrm{NHR} + 2\,\mathrm{R'NH_2} \rightarrow \mathrm{RNH}\overset{\overset{\mathrm{R'N}}{\|}}{\mathrm{C}}-\overset{\overset{\mathrm{NR'}}{\|}}{\mathrm{C}}\mathrm{NHR} + 2\,\mathrm{NH_3}$$

The first possibility was realized by the isolation in yields of 20–80% of tetramethyl-, tetraethyl-, tetra-*n*-propyl-, tetra-*n*-butyl, and tetraisobutyl-oxamidines from reaction mixtures containing the corresponding disubstituted oxamidines and primary amines.

When amines with different alkyl groups were used, however, instead of replacement of hydrogen by alkyl, interchange of alkyl groups between amine and

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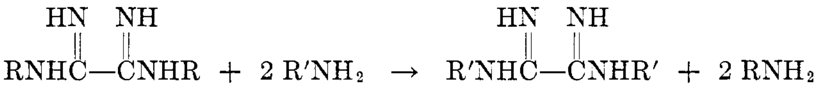
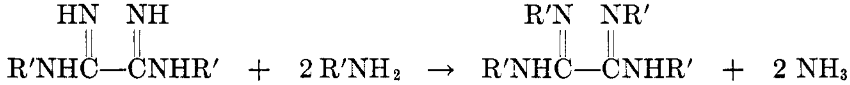
oxamidine occurred in every case where the formula weight of the alkyl group in the amine was greater than that in the oxamidine.



$$\mathrm{RNH}\overset{\mathrm{HN}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{NH}}{\overset{\|}{\mathrm{C}}}\mathrm{NHR} + 2\,\mathrm{R'NH_2} \rightarrow \mathrm{R'NH}\overset{\mathrm{HN}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{NH}}{\overset{\|}{\mathrm{C}}}\mathrm{NHR'} + 2\,\mathrm{RNH_2}$$

Thus from diethyloxamidine and isopropylamine there was obtained a 40% yield (as hydrochloride) of diisopropyloxamidine, and from diethyloxamidine and aniline there was isolated diphenyloxamidine, the "cyanoaniline" reported by Hoffmann in 1848 (2).

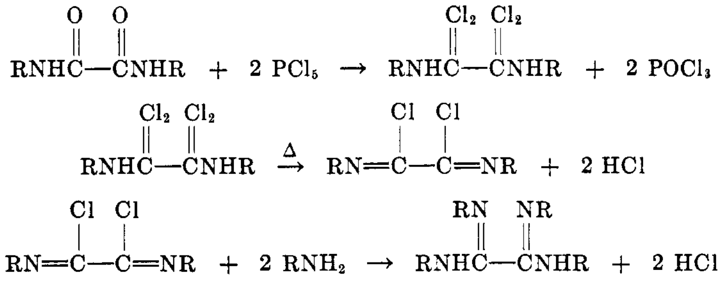
In many cases the exchange of groups was followed by conversion of the new oxamidine to a tetrasubstituted derivative of the heavy alkyl group.



$$\mathrm{R'NH}\overset{\mathrm{HN}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{NH}}{\overset{\|}{\mathrm{C}}}\mathrm{NHR'} + 2\,\mathrm{R'NH_2} \rightarrow \mathrm{R'NH}\overset{\mathrm{R'N}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{NR'}}{\overset{\|}{\mathrm{C}}}\mathrm{NHR'} + 2\,\mathrm{NH_3}$$

Table I lists the results of 27 reactions. In all cases except those noted, the oxamidines were used in the form of their hydrochlorides since the yield of product was considerably better under those conditions than when the free base was used.

Carbon, hydrogen, and nitrogen analyses were carried out on all tetra compounds. In addition the tetraethyl and tetrapropyl derivatives were synthesized for comparison by treatment of the corresponding imidic chlorides with the alkyl amine.



$$\mathrm{RNH}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{NHR} + 2\,\mathrm{PCl_5} \rightarrow \mathrm{RNH}\overset{\mathrm{Cl_2}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{Cl_2}}{\overset{\|}{\mathrm{C}}}\mathrm{NHR} + 2\,\mathrm{POCl_3}$$

$$\mathrm{RNH}\overset{\mathrm{Cl_2}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{Cl_2}}{\overset{\|}{\mathrm{C}}}\mathrm{NHR} \xrightarrow{\Delta} \mathrm{RN}{=}\overset{\mathrm{Cl}}{\overset{|}{\mathrm{C}}}-\overset{\mathrm{Cl}}{\overset{|}{\mathrm{C}}}{=}\mathrm{NR} + 2\,\mathrm{HCl}$$

$$\mathrm{RN}{=}\overset{\mathrm{Cl}}{\overset{|}{\mathrm{C}}}-\overset{\mathrm{Cl}}{\overset{|}{\mathrm{C}}}{=}\mathrm{NR} + 2\,\mathrm{RNH_2} \rightarrow \mathrm{RNH}\overset{\mathrm{RN}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{NR}}{\overset{\|}{\mathrm{C}}}\mathrm{NHR} + 2\,\mathrm{HCl}$$

This is an application to aliphatic compounds of a reaction discovered by Bauer (3) for the preparation of tetraaryloxamidines.

Disubstituted compounds formed by exchange reactions were identified by mixed melting point with compounds produced directly from cyanogen and amine (1).

Reactions 26 and 27 were carried out in the hope of obtaining secondary amine derivatives either by substitution or exchange. The reactants were recovered without change in both cases.

Generally speaking, the tetraalkyloxamidines were obtained in the form of white, silky or fibrous crystals. The two lower members were extremely soluble in water, less so in ethanol, and only slightly soluble in ether and petroleum ether. The water-solubility decreased with increasing molecular weight; the ether solubility increased.

All the compounds were stable to moderate heating (100°), could be boiled for short periods with water without decomposition, and in the one case investigated would not undergo ammonolysis on prolonged boiling with alcoholic ammonia.

TABLE I

Reactions of Oxamidines with Amines

REACTANTS		YIELD, %	PRODUCT	M.P., °C.
Oxamidine hydrochloride	Amine			
1. Dimethyl	Methyl	70	Tetramethyloxamidine	243–245 dec.
2. Diethyl	Ethyl	21	Tetraethyloxamidine	150
3. Di-*n*-propyl	*n*-Propyl	83	Tetrapropyloxamidine	110
4. Diisopropyl	Isopropyl	0	Oxamidine recovered	
5. Di-*n*-butyl	*n*-Butyl	76	Tetrabutyl oxamidine	86
6. Di-*sec*-butyl	*sec*-Butyl	0	Oxamidine recovered	
7. Diisobutyl	Isobutyl	V. low	Tetraisobutyloxamidine	79–80
8. Di-*n*-amyl	*n*-Amyl	[a]		
9. Diethyl (base)	Ethyl	V. low	Tetraethyloxamidine	150
10. Di-*n*-propyl (base)	*n*-Propyl	V. low	Tetrapropyloxamidine	110
11. Di-*n*-butyl (base)	*n*-Butyl	18	Tetrabutyloxamidine	86
12. Diisobutyl (base)	Isobutyl	V. low	Tetraisobutyloxamidine	79–80
13. Dimethyl	Ethyl	25	Tetraethyloxamidine	150
14. Diethyl	*n*-Propyl	33	Tetrapropyloxamidine	110
15. Diethyl	Isopropyl	40	Diisopropyloxamidine hydrochloride	287–290 dec.
16. Diethyl	*n*-Butyl	90	Tetrabutyloxamidine	86
17. Di-*n*-propyl	*n*-Butyl	90	Tetrabutyloxamidine	86
18. Dimethyl	Isobutyl	32	Tetraisobutyloxamidine	79–80
19. Diethyl	Isobutyl	17[b]	Diisobutyloxamidine hydrochloride	290 dec.
20. Diethyl	Isobutyl	43[c]	Tetraisobutyloxamidine	79–80
21. Diethyl	*sec*-Butyl	V. low	Di-*sec*-butyloxamidine hydrochloride	295 dec.
22. Diethyl	*n*-Amyl		Tarry mass	
23. Di-*n*-amyl	*n*-Propyl		Tarry mass	
24. Diethyl	Aniline	73	Diphenyloxamidine	210
25. Di-*n*-amyl	Aniline	V. low	Diphenyloxamidine	210
26. Diethyl	Diethyl	0	Oxamidine recovered	
27. Diethyl	Di-*n*-butyl	0	Oxamidine recovered	

[a] The product was impossible to purify. The physical appearance of the impure material resembled that of other tetra compounds. [b] Reaction time, five minutes. [c] Reaction time, one hour.

The tetramethyl derivative differed from the remainder of the series in possessing an unusually high melting point and in the granular appearance of its crystals. The latter property may have resulted from the fact that it was the only compound that was purified by ethanol recrystallization.

It is noteworthy that in certain cases the yield of tetra compound was better from an exchange reaction than from a substitution process.

EXPERIMENTAL

SUBSTITUTION REACTIONS

sym-Tetramethyloxamidine. An excess of methylamine was introduced into a pressure bottle containing 3.0 g. (0.016 mole) of *sym*-dimethyloxamidine dihydrochloride and allowed to stand at room temperature for 24 hours. The bottle was cooled in a Dry-Ice chest until the contents became solid, whereupon 20 ml. of ethanol was added to dissolve methylamine hydrochloride and the mixture filtered. The solid residue was recrystallized from hot ethanol resulting in granular crystals, m.p. 243–245° with decomposition; yield, 1.6 g. or 70%.

Anal. Calc'd for $C_6H_{14}N_4$: C, 50.7; H, 9.9; N, 39.4.

Found: C, 50.7; H, 10.3; N, 39.8.

sym-Tetraethyloxamidine. (*a*) An excess of ethylamine was introduced into a pressure bottle containing 2.5 g. (0.012 mole) of *sym*-diethyloxamidine dihydrochloride and allowed to stand at room temperature for 12 hours. Cooling in an ice-bath caused the separation of a solid which was filtered and extracted with ether, leaving a residue of ethylamine hydrochloride. The ether extract on evaporation gave white crystals, which were taken up in ether and recovered by slow evaporation several times to remove traces of ethylamine. The final product was in the form of white, silky, fibrous crystals melting at 150°, easily soluble in ether, alcohol, and water. The yield of pure material was 0.5 g. or 21%.

Anal. Calc'd for $C_{10}H_{22}N_4$: C, 60.6; H, 11.1; N, 28.3.

Found: C, 60.0; H, 11.1; N, 28.2.

(*b*) An excess of ethylamine was reacted in a pressure bottle at room temperature with 4.3 g. (0.03 mole) of *sym*-diethyloxamidine to give a very small yield of silky, fibrous crystals melting at 150°.

sym-Tetra-n-propyloxamidine. (*a*) An excess of *n*-propylamine was refluxed with 3 g. (0.013 mole) of *sym*-di-*n*-propyloxamidine dihydrochloride for five hours. The mixture was cooled, filtered to remove precipitated propylamine hydrochloride, and poured into 200 ml. of water. An oily mass of crystals separated which was dried and recrystallized from petroleum ether. The product in the form of white, silky, fibrous crystals, melted at 110° and weighed 2.5 g., an 80% yield.

Anal. Calc'd for $C_{14}H_{30}N_4$: C, 66.2; H, 11.8; N, 22.0.

Found: C, 66.1; H, 12.3; N, 22.1.

(*b*) An excess of *n*-propylamine refluxed with 3 g. (0.018 mole) of *sym*-di-*n*-propyloxamidine for five hours gave a very small yield of silky, fibrous crystals melting at 110°.

sym-Tetra-n-butyloxamidine. (*a*) An excess of *n*-butylamine was refluxed with 3 g. (0.011 mole) of *sym*-di-*n*-butyloxamidine dihydrochloride for three hours and the product worked up as described above (see *n*-propyl). A 76% yield of white, silky, fibrous crystals melting at 86° resulted.

Anal. Calc'd for $C_{18}H_{38}N_4$: C, 69.7; H, 12.3; N, 18.1.

Found: C, 69.7; H, 12.4; N, 18.4.

(*b*) An excess of *n*-butylamine was refluxed with 4.9 g. (0.025 mole) of *sym*-di-*n*-butyloxamidine in 200 ml. of ether for 24 hours. After removal of the ether by distillation the liquid residue was poured into 200 ml. of water producing a mass of fibrous crystals. Recrystallization from ether gave an 18% yield of material melting at 86°.

sym-Tetraisobutyloxamidine. (*a*) An excess of isobutylamine was refluxed with 3.0 g. (0.011 mole) of *sym*-diisobutyloxamidine dihydrochloride for 12 hours. After cooling, the mixture was poured into ice-water and the heavy, yellow mass which separated was filtered off. Recrystallization from petroleum ether gave fine white needles, m.p. 79–80°; but the yield of pure material was very low.[4]

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[4] Better yields of this compound were obtained by the exchange reactions 18 and 20.

Anal. Calc'd for $C_{18}H_{38}N_4$: C, 69.7; H, 12.3; N, 18.1.
Found: C, 69.5; H, 12.7; N, 18.3.

(*b*) An excess of isobutylamine refluxed for two hours with 2.0 g. (0.007 mole) of *sym*-diisobutyloxamidine gave a very low yield of material melting at 79–80°.

UNSUCCESSFUL REACTIONS

Sym-diisopropyloxamidine dihydrochloride with isopropylamine. An excess of isopropylamine was refluxed with 2 g. (0.01 mole) of *sym*-diisopropyloxamidine dihydrochloride for 20 hours. Crystals of isopropylamine hydrochloride were recovered from the cooled mixture. The filtrate, allowed to evaporate slowly, gave a heavy, oily residue which would not crystallize. It was taken up in alcohol and treated with dry hydrogen chloride. The solid formed, melted with decomposition at 290° and gave no depression of melting point when mixed with *sym*-diisopropyloxamidine dihydrochloride. The recovery of the oxamidine was about 90%.

Sym-di-sec-butyloxamidine dihydrochloride with sec-butylamine. An excess of *sec*-butylamine refluxed with *sym*-di-*sec*-butyloxamidine dihydrochloride for 3 hours gave crystals of *sec*-butylamine hydrochloride but no tetra-substitution product. The filtrate, treated with alcohol and hydrogen chloride was found to contain only *sym*-di-*sec*-butyloxamidine dihydrochloride.

Sym-di-n-amyloxamidine dihydrochloride with n-amylamine. An excess of *n*-amylamine was refluxed with 3 g. (0.01 mole) of *sym*-di-*n*-amyloxamidine dihydrochloride for 12 hours. The mixture was poured into ice-water and the tarry mass which resulted was extracted with ether. Evaporation gave a solid made up of crystals and tar. Repeated attempts at purification failed to give a product sufficiently clean to justify analysis or the measurement of physical constants.

EXCHANGE REACTIONS

Tetraethyloxamidine from dimethyloxamidine hydrochloride and ethylamine. An excess of ethylamine was placed in a pressure bottle containing 1.1 g. (0.006 mole) of *sym*-dimethyloxamidine dihydrochloride and allowed to stand at room temperature for 24 hours. Cooling in ice caused the separation of crystals which on recrystallization from ether melted at 150°. A mixed melting point determination proved them to be tetraethyloxamidine; yield, 0.3 g. or 25%.

Tetrapropyloxamidine from diethyloxamidine hydrochloride and n-propylamine. An excess of *n*-propylamine was refluxed with 2 g. (0.01 mole) of *sym*-diethyloxamidine dihydrochloride for 3 hours. The mixture was cooled, separated from crystals of amine hydrochloride which deposited, and poured into water. The solid which was produced was recrystallized from petroleum ether giving crystals that melted at 110°. No depression of melting point resulted by admixture with *sym*-tetra-*n*-propyloxamidine. The yield was 33%.

Diisopropyloxamidine hydrochloride from diethyloxamidine hydrochloride and isopropylamine. An excess of isopropylamine was refluxed with 1 g. (0.005 mole) of *sym*-diethyloxamidine dihydrochloride for 12 hours. The reaction mixture was cooled in an ice-bath, filtered to remove amine hydrochlorides, and allowed to evaporate. Attempts to crystallize the oily residue were ineffective, consequently, it was taken up in alcohol and treated with anhydrous hydrogen chloride. A 40% yield of *sym*-diisopropyloxamidine dihydrochloride melting with decomposition at 287–290° was obtained.

Tetrabutyloxamidine from diethyloxamidine hydrochloride and n-butylamine. An excess of *n*-butylamine refluxed for 5 hours with 2 g. (0.01 mole) of *sym*-diethyloxamidine dihydrochloride gave a 90% yield of *sym*-tetrabutyloxamidine (m.p. 86°) when the reaction mixture was worked up in the usual way. Identification was made by mixed melting point.

Tetrabutyloxamidine from dipropyloxamidine hydrochloride and n-butylamine. A 90% yield of *sym*-tetrabutyloxamidine was obtained from the refluxing of *sym*-di-*n*-propyloxamidine dihydrochloride with excess *n*-butylamine.

Tetraisobutyloxamidine from dimethyloxamidine hydrochloride and isobutylamine. An excess of isobutylamine was refluxed with 2.0 g. (0.01 mole) of *sym*-dimethyloxamidine dihydrochloride for two hours and the mixture poured into cold water. The yellow solid which separated was recrystallized from petroleum ether giving fine, white needles melting at 79–80° which gave no melting point depression with a sample of tetraisobutyloxamidine. The yield was 32%.

Diisobutyloxamidine hydrochloride from diethyloxamidine hydrochloride and isobutylamine. An excess of isobutylamine was refluxed with 2.5 g. (0.012 mole) of *sym*-diethyloxamidine dihydrochloride for *five minutes.* The resulting mixture was diluted with ether and the insoluble amine hydrochlorides filtered off. Evaporation of the filtrate left an oily liquid which was taken up in alcohol and saturated with anhydrous hydrogen chloride. White crystals melting at 290° with decomposition, and giving no melting point depression with *sym*-diisobutyloxamidine dihydrochloride were obtained. The yield was 17%.

Tetraisobutyloxamidine from diethyloxamidine hydrochloride and isobutylamine. An excess of isobutylamine was refluxed with 3.0 g. (0.015 mole) of *sym*-diethyloxamidine dihydrochloride *for one hour.* The resulting mixture was poured into cold water and a heavy yellow mass separated weighing about 2 g. (43% yield). Recrystallization from petroleum ether gave fine white needles melting at 79–80° and giving no melting point depression with a sample of tetraisobutyloxamidine.

Di-sec-butyloxamidine hydrochloride from diethyloxamidine hydrochloride and sec-butylamine. Sym-diethyloxamidine dihydrochloride refluxed for 2 hours with excess *sec*-butylamine gave a very low yield of *sym*-di-*sec*-butyloxamidine isolated as the hydrochloride.

Diphenyloxamidine from diethyloxamidine hydrochloride and aniline. Three grams (0.014 mole) of *sym*-diethyloxamidine dihydrochloride in 80 ml. of alcohol was refluxed for 3 hours with 3 g. (0.032 mole) of aniline. Crystals were formed as the solution cooled. These, recrystallized from benzene, melted at 210° and gave no melting point depression when mixed with *sym*-diphenyloxamidine prepared from cyanogen and aniline (2). The yield was 73%.

Diphenyloxamidine from diamyloxamidine hydrochloride and aniline. A mixture of *sym*-diamyloxamidine dihydrochloride, alcohol, and aniline was refluxed as above. Three-days standing was required before crystals of *sym*-diphenyloxamidine (m.p. 210°) appeared. The yield was very low.

Unsuccessful reactions. The following combinations gave tarry masses from which no crystalline product could be isolated: *sym*-diethyloxamidine dihydrochloride and *n*-amylamine, *sym*-di-*n*-amyloxamidine dihydrochloride and *n*-propylamine. The original oxamidine was recovered when *sym*-diethyloxamidine dihydrochloride was refluxed (*a*) for 12 hours with excess of the secondary amine, di-*n*-butylamine and (*b*) for 2 days with the secondary amine, diethylamine.

sym-Tetraethyloxamidine from diethyloxamide (3). Into a flask fitted with a fractionating-column was introduced 200 ml. of dry toluene, 3.6 g. (0.025 mole) of *sym*-diethyloxamide, and 10.4 g. (0.05 mole) of phosphorus pentachloride. Hydrogen chloride was evolved slowly and the mixture turned yellow. After about one-half hour a water aspirator was attached to the apparatus and heat was applied gradually until the distillation temperature was reached; most of the phosphorus oxychloride and toluene was removed in this way. (The presence of toluene allowed the phosphorus oxychloride to be distilled off at a temperature below the decomposition temperature of the imidic chloride.)

The residue was cooled in Dry Ice and an excess of anhydrous ethylamine was introduced. A tarry crystalline mass formed as the mixture came to room temperature and the unreacted ethylamine evaporated. Triethylamine proved to be the best medium for the separation of the product from tarry impurities, first by simple agitation and decantation, later by extraction of the tarry residue with hot solvent. A 34% yield of silky, fibrous crystals melting at 150° was obtained.

sym-Tetrapropyloxamidine from dipropyloxamide. Treatment of *sym*-di-*n*-propyloxamide with phosphorus pentachloride and *n*-propylamine in the manner described above gave a low yield of a product melting at 110°.

SUMMARY

Symmetrically disubstituted oxamidines react with primary amines either to yield *sym*-tetrasubstituted oxamidines by substitution of alkyl for hydrogen or to yield a second disubstituted oxamidine by exchange of alkyl groups.

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REFERENCES

(1) WOODBURN, MOREHEAD, AND CHEN, *J. Org. Chem.*, preceding paper.
(2) HOFFMANN, *Ann.*, **66**, 130 (1848).
(3) BAUER, *Ber.*, **40**, 2650 (1907).