Anal. Calcd. for $C_2Cl_6S_2$: S, 21.2; mol. wt., 301. Found: S, 20.6; mol. wt., 290.

The distillation residue contained methyl dodecanedioate, 12.3 g. (19.5%).

Reaction of Cyclohexanone Peroxide with *o*-Nitrobenzenesulfenyl Chloride.—To a 500-ml. reaction flask was charged 50 g. (0.18 mole) of powdered ferrous sulfate, 75 ml. of methanol, and 7 ml. of concd. sulfuric acid. At −20° a solution containing 200 ml. of ether, 37 g. (0.19 mole) of *o*-nitrobenzenesulfenyl chloride, and 22.8 g. (0.17 mole) of commercial cyclohexanone peroxide was added to the ferrous sulfate mixture with stirring. After stirring the reaction product an additional 15 min., 100 ml. of water was added.

Crystalline *o*-nitrophenyl disulfide 6.7 g. (25%) was separated by filtration. The melting point and mixed melting point showed the material to be *o*-nitrophenyl disulfide.

The ether phase was evaporated and the residue esterified with methanol and distilled: methyl ω-chlorocaproate, 5.5 g. (20%); methyl dodecanedioate, 1.9 g. (10%).

Preparation of Methyl Methylmercaptocaproate.—The procedure was similar to that used for the reaction of carbon tetrachloride and cyclohexanone peroxide. To the peroxide solution (0.49 mole) was added 25.7 g. (0.535 mole) of methyl mercaptan followed by the dropwise addition of ferrous salt solution. Following the esterification procedure, the reaction product was distilled through a 12-in. Vigreux column. No attempt was made to isolate the methyl disulfide which may have been present. Crude methyl caproate 16.6 g. (26.1%) was collected at 145–149°. At 117 to 129°/15 mm., 9.1 g. (11.5%) of methyl methylmercaptocaproate was collected.

Anal. Calcd. for $C_8H_{16}O_2S$: S, 18.1; mol. wt., 176; sapon. equiv., 176. Found: S, 18.6; mol. wt., 172; sapon. equiv., 185.

To confirm the location of the methylmercapto group in the terminal position, the methyl methylmercaptocaproate was hydrolyzed and the free acid converted to the phenylhydrazide derivative,[13] m.p. 78°. A mixed melting point with the phenylhydrazide prepared from the reaction product of sodium methyl mercaptide and ω-chlorocaproic acid was not depressed.

Methyl dodecanedioate was isolated in 21% yield.

Reduction of Cyclohexanone Peroxide in the Presence of Benzenethiol.—Ferrous salt reduction of 0.49 mole of cyclohexanone peroxide in the presence of benzenethiol (0.53 mole) was carried out. Filtration of the reaction mixture gave 25.4 g. (46.6%) of phenyl disulfide. After recrystallization from ethanol this material did not depress the melting point of a known sample of phenyl disulfide.

Isolation of the other reaction products was carried out by esterification and distillation: methyl caproate, 6.3 g. (9.7 %); methyl phenylmercaptocaproate, (3.2%) collected at 98–102° at 0.01 mm. Hydrolysis of this ester gave phenylmercaptocaproic acid.

Anal. Calcd. for $C_{12}H_{16}O_2S$: S, 14.3; neut. equiv., 224. Found: S, 12.7; neut. equiv., 216.

Methyl dodecanedioate, 22.0 g. (34.1%).

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[13] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, New York, 1950, p. 158.

Extent of Formaldehyde Reaction with Selected Amides[1]

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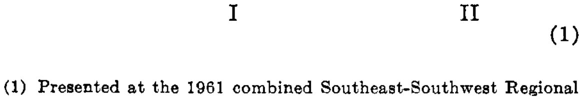
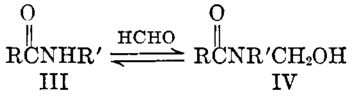
Various formamides and acetamides of the general structures $RCONH_2$, $RCONHR'$, and RCONH-X-NHCOR, where X = alkylene or substituted alkylene, were treated with an excess of formaldehyde to produce the *N*-methylol derivatives. The extent of the reaction was determined by titration of the unchanged formaldehyde. Contrary to previous reports, methylolation of *N*-substituted amides goes to 50–100% of completion in many of the cases studied. Methylolation is more nearly complete with the bisformamides than with the bisacetamides. Five new bisamides were synthesized by the reaction of diamines with esters.

The industrial uses of amide-formaldehyde reaction products in textile treating, resin manufacturing, etc., are widespread. Methylolation (or hydroxymethylation) of an unsubstituted amide can theoretically proceed through the following steps:



$$R\overset{\overset{O}{\|}}{C}NH_2 \xrightleftharpoons{HCHO} \underset{I}{R\overset{\overset{O}{\|}}{C}NHCH_2OH} \xrightleftharpoons{HCHO} \underset{II}{R\overset{\overset{O}{\|}}{C}N(CH_2OH)_2} \qquad (1)$$

or in case of substituted amide:



$$\underset{III}{R\overset{\overset{O}{\|}}{C}NHR'} \xrightleftharpoons{HCHO} \underset{IV}{R\overset{\overset{O}{\|}}{C}NR'CH_2OH} \qquad (2)$$

Extensive work by Einhorn and co-workers[3a,b] in the early 1900's indicated that reaction 1 generally proceeds only to the mono derivative and reaction 2, where R′ = alkyl, generally fails to occur. A later review by Walker[4] presented substantiation of this earlier work, but melamine and some cyclic ureas were shown to be exceptions and could be fully methylolated. Textile finishing in the wash-wear field would scarcely have pro-

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(1) Presented at the 1961 combined Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, La., December 7-9, 1961.

(2) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

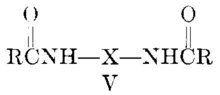
(3) (a) A. Einhorn *et al.*, *Ann.*, **343**, 207 (1905); (3) (b) *ibid.*, **361**, 113 (1908).

(4) J. F. Walker, "Formaldehyde," 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1953, p. 290.

gressed to its present point,[5] if cyclic ureas, a substituted amide type, could not be methylolated as shown in equation 2. In general, the *N*-methylol derivatives of the amide types discussed above are unstable products which release formaldehyde on heating, whereas the ethers of these derivatives are more stable.

The exceptions noted by Walker are quite different from the aliphatic, linear amides used by Einhorn in his studies. However, in recent work[6,7] at this Laboratory cellulose ethers of aliphatic, linear methylolamides have been formed, *i.e.*, a dicellulose ether of bis(hydroxymethyl)formamide and monocellulose ethers of *N*-methylol derivatives of *N*-methylacetamide and *N*-methylformamide. In order to form these ethers efficiently, complete methylolation, as illustrated by II and IV, is required. Other workers[8] in a concurrent publication also disputed Einhorn's conclusion by reporting the reaction of formaldehyde with *N*-alkylamides to form products (postulated as the *N*-methylol derivative) which were converted into *N*-alkyl-*N*-chloromethyl amides.

In this work the extent of the reaction in alkaline solution of formaldehyde with formamides and acetamides has been studied. The compounds include bisformamides and bisacetamides of the type:



$$\mathrm{R\overset{O}{\overset{\|}{C}}NH-X-NH\overset{O}{\overset{\|}{C}}R}$$

V

The amides needed for this work (see Table I), some of which were not readily available, were prepared by reactions run at atmospheric pressures.[9] Five bisamides of type V, believed to be new compounds, and their properties are shown in Table II. All are stable, water-soluble materials and were prepared by the acylation of the diamine with an excess of the required ester.

These acylations are generally considered to be initiated by attack of the nucleophilic nitrogen on the carbonyl carbon atom. Thus, it was not unexpected[10] to find that the formic esters were more reactive with a given diamine than were the acetic esters.

The large differences noted, however, in several comparable syntheses are interesting, particularly since the reaction mixtures containing excess ester were able to reflux at higher temperatures when the solvent-reactant was ethyl acetate rather than methyl formate (Δb.p. = 46°). For example, ethylene- and 1,3-propanebisformamide were prepared from methyl formate and the required diamine in almost quantitative yield, whereas ethylene- and 1,3-propanebisacetamide (from ethyl acetate and the same diamines) were prepared in yields of only 11% and 20%, respectively. Similarly, propylenebisformamide was isolated from refluxing propylenediamine and methyl formate (12% yield) or ethyl formate (30% yield), but propylenebisacetamide was not isolated from refluxing propylenediamine and ethyl acetate.

TABLE I

YIELDS FROM PREPARATION OF AMIDES AND EXTENT OF HCHO REACTION

Monoamides:	$\mathrm{R\overset{O}{\overset{\|}{C}}-\overset{H}{N}R'}$	Yield	Method[a]	Reaction Ratio, HCHO/NH[b]
R	R'			
H	H	. . .	. .	0.84
H	CH_3	. . .	. .	0.63
CH_3	H	. . .	. .	0.73
CH_3	CH_3	. . .	. .	0.79
Bisformamides:	$\mathrm{H\overset{O}{\overset{\|}{C}}-\overset{H}{N}-X-\overset{H}{N}-\overset{O}{\overset{\|}{C}}H}$			
X				
CH_2		32%	B	0.96
CH_2CH_2		95%	A[c]	1.00
CH_2CHCH_3		12%	A[d]	0.86
$CH_2CH_2CH_2$		92%	A	0.95
$CH_2CHOHCH_2$		95%	A	0.85
$HCON(CH_2CH_2CH_2)_2$		100%	A	0.97
Bisacetamides:	$\mathrm{CH_3\overset{O}{\overset{\|}{C}}-\overset{H}{N}-X-\overset{H}{N}-\overset{O}{\overset{\|}{C}}CH_3}$			
X				
CH_2		16%	B	0.50
$CHCH_3$		38%	B	0.32
CHC_2H_5		35%	B[e]	0.29
CH_2CH_2		11%	A[f]	0.50
$CH_2CH_2CH_2$		20%	A	0.48

[a] A, reaction of the suitable diamine with methyl formate or ethyl acetate; B, refluxing of the suitable aldehyde with formamide or acetamide. [b] Values represent HCHO reacted for each amido hydrogen theoretically replaceable (as in equations 1 and 2). Precision considered to be within ±0.05. [c] Acylation of ethylenediamine with formamide produced a 72% yield. [d] Acylation with ethyl formate increased the yield to 30%. [e] Benzylidenebisacetamide prepared in 17% yield was not methylolated because of insolubility. [f] Acylation of ethylenediamine with acetamide produced a 59% yield.

The amides in Table I were treated with an excess of formaldehyde in an attempt to force complete methylolation. The extent of the reaction was determined by titrating at equilibrium the unreacted or free formaldehyde according to an accepted procedure.[11] Isolation of methylol derivatives was attempted and is also discussed.

Methylolation (see Table I) of *N*-alkyl substituted amides (equation 2) is shown to occur, in agreement with recent findings.[6-8] In two of these three examples the equilibrium is such that more IV is present than III. The methylolation of formamide

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[5] H. Tovey, *Textile Research J.*, **31**, 219 (1961).

[6] S. L. Vail, J. G. Frick, Jr., P. J. Murphy, Jr., and J. D. Reid, *Am. Dyestuff Reptr.*, **50**, 437 (1961).

[7] W. A. Reeves, S. L. Vail, J. G. Frick, Jr., presented at the Tenth Chemical Finishing Conference, Washington, D. C., November 8-9, 1961.

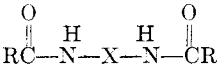
[8] H. Bohme, A. Dick, and G. Dreisen, *Ber.*, **94**, 1879 (1961).

[9] Although a large number of amides have been prepared from diamines there appears to be a surprising absence of studies of the chemistry of these syntheses. See C. L. Agre, G. Dinga, and R. Pflaum, *J. Org. Chem.*, **21**, 561 (1956).

[10] M. Gordon, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **70**, 1946 (1948).

[11] J. C. Morath and J. T. Woods, *Anal. Chem.*, **30**, 1437 (1958).

Table II
Properties of Bisamides



$$RC(=O)-N(H)-X-N(H)-C(=O)R$$

R	X	M.P.	Mol. Wt.		Nitrogen, %	
			Calcd.	Found	Calcd.	Found
H	CH_2CHCH_3	70–72°	130	131	21.53	21.52
H	$CH_2CH_2CH_2$	Oil	130	130	21.53	21.36
H	$CH_2CHOHCH_2$	Oil	146	142	19.17	19.29
H	$HCON(CH_2CH_2CH_2)_2$	Oil	215	215	19.52	19.26
CH_3	$CH_2CH_2CH_2$	102–105°	158	158	17.71	17.69

and acetamide appears to proceed to II in equation 1 and provides further examples of dimethylolation of an unsubstituted amide.

The methylolation (see Table I) of the bisamides (V) is considered to be another example of equation 2. The data in Table I indicate that bisformamides as a class react with two moles of formaldehyde, whereas the bisacetamides react with only one. Substitution on the alkylene group of the bisamides decreases the degree of methylolation slightly. The contrast between the behavior of the bisformamides and the bisacetamides is quite striking, particularly when compared with that of the monoamides.

Crowe and Lynch[12] have conducted kinetic studies of formaldehyde addition to acetamide and benzamide. These workers propose a mechanism whereby the unhydrated formaldehyde combines with the anion of the amide. An electron-donating group (such as methyl) causes decreased proton dissociation and anion formation affecting the rate of the reaction but not the equilibrium. In a similar manner, other workers[13] studied the reaction of other amides with formaldehyde and came to the same conclusion.

Accordingly, formamides should be more reactive than acetamides, but this does not fully explain why only one molar equivalent or less of formaldehyde adds to a bisacetamide when there are theoretically two sites for the reaction. Extension of the unsubstituted alkylene portion of the bisamides from one to three carbons had essentially no effect on the extent of formaldehyde addition. Thus, inductive effects of the *N*-substituents are negligible for the formaldehyde addition. The same conclusion is drawn from the data concerning the methylolation of the four selected monoamides.

For methylolation of the monoamides, steric factors appear to be negligible. However, with the bisformamides a slight but significant decrease in formaldehyde addition is noted in the two cases where the alkylene group was substituted. For methylolation of the bisacetamides, steric factors introduced by substitution of the alkylene group appear to contribute to the reduction of the extent of formaldehyde addition. Thus, it is concluded that steric factors are affecting the reaction when the alkylene portion of the bisamide is substituted.

The larger effect noted in the formaldehyde addition to the bisamides, that is, the addition of only one molar equivalent or less of formaldehyde to the bisacetamide, is not readily explainable. The substitution of the methyl in the acyl group can theoretically decrease the reactivity of the amide through both steric and electronic effects. However, this combined effect is not apparent in the monoamides. Also, hydrogen bonding of the amide or methylolated amide may be a factor. *N*-Substituted amides are known[14,15] to form relatively stable hydrogen bonds. In a similar case Kogon[16] has suggested that because of intramolecular hydrogen bonding, the allophanate molecule is unreactive to phenyl isocyanate.

As shown by the data in Table I, ethylenebisformamide (VI) adds two moles of formaldehyde, whereas ethylenebisacetamide (VII) adds one. The infrared spectra of these methylol derivatives were examined and compared to those of the bisamides to establish more fully their structures. The presence of the *N*,*N'*-bis(hydroxymethyl) derivative of VI was indicated by several factors: (a) a sharp NH band at 3.07 μ in VI was changed to a sharp OH band at 3.10 μ; (b) the amide II band of VI at 6.46 μ disappeared; and (c) the OH bending band at 9.36 μ was present only in the formaldehyde adduct. Similarly, presence of the *N*-hydroxymethyl derivative of VII was indicated by (a) combined OH and NH bands at 3.05 and 3.08 μ, whereas VII had a sharp NH band at 3.05 μ; (b) amide II band at 6.40 μ of VII significantly decreased in intensity; and (c) OH band at 9.47 μ present only in the formaldehyde adduct. At least one band of VI and VII was not present in the spectra of the methylolated products, indicating an equilibrium far to the right.

Experimental[17]

Methylenebisformamide,[18] m.p. 141–144°, was prepared in 32% yield from formaldehyde and formamide. Greatly

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[12] G. A. Crowe, Jr., and C. C. Lynch, *J. Am. Chem. Soc.*, **72**, 3622 (1950).

[13] J. Ugelstad and J. de Jonge, *Rec. trav. chim.*, **76**, 919 (1957).

[14] S. Glasstone, "Textbook of Physical Chemistry," 2nd ed., D. Van Nostrand Co., Inc., New York, N. Y., 1946, p. 115.

[15] S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Org. Chem.*, **26**, 2343 (1961).

[16] I. C. Kogon, *J. Am. Chem. Soc.*, **79**, 2253 (1957).

[17] All melting points are uncorrected. Infrared spectra were obtained from potassium bromide disks with a Perkin-Elmer spectrophotometer, Model 21.

[18] P. Knudsen, *Ber.*, **47**, 2698 (1914).

improved yields are noted in a recent publication[19] where hexamethylenetetramine was the source of formaldehyde and the mother liquor was reused as solvent; lit.,[18] m.p. 142–143°.

Methylenebisacetamide, m.p. 196–198° in yield of 16%, **ethylidenebisacetamide,** m.p. 178–182° in yield of 38%, **propylidenebisacetamide,** m.p. 191–194° in yield of 35%, and **benzylidenebisacetamide,** m.p. 235–239° in yield of 17%, were prepared[20] by refluxing 1 mole of the required aldehyde with 2 moles of acetamide and 0.2 mole of acetic acid for about 4 hr. The products were recrystallized from a 1:1 ethanol–acetone mixture.

Bisamides from the Reaction of Diamines and Esters.—As a general procedure, the diamine was added slowly to an excess of the ester cooled in ice. The solution was refluxed for 6–10 hr. and, after standing overnight, the products were isolated by filtration or evaporation of volatile materials with heat and vacuum.

Ethylenebisformamide (VI) was prepared in 95% yield by refluxing ethylenediamine and methyl formate. The solids obtained by filtration were recrystallized from ethyl acetate or ethyl alcohol; m.p. 108–110°; lit.,[21] m.p. 110–111°.

Propylenebisformamide was prepared in only 12% yield by refluxing propylenediamine and methyl formate. With ethyl formate the yield was increased to 30%. The filtered product was recrystallized from ethyl alcohol and melted at 70–72°.

Anal. Calcd. for $C_5H_{10}N_2O_2$: C, 46.14; H, 7.74; N, 21.53; mol. wt., 130. Found: C, 46.11: H, 7.64; N, 21.52; mol. wt. (by osmometer), 131.

1,3-Propanebisformamide (VIII) was prepared in 92% yield by refluxing 1,3-propanediamine and methyl formate. Product was isolated as the residue in a vacuum distillation with a maximum pot temperature of 175° (5 mm.). The product was a yellowish oil.

Anal. Calcd. for $C_5H_{10}N_2O_2$: N, 21.53; mol. wt., 130. Found: N, 21.36; mol. wt. (by osmometer), 130.

***N,N*-Bis(3-formamidopropyl)formamide** was prepared in 100% yield by refluxing 3,3′-iminobispropylamine and methyl formate. Isolation procedure was the same as for VIII.

Anal. Calcd. for $C_9H_{17}N_3O_3$: N, 19.52; mol. wt., 215. Found: N, 19.26; mol. wt. (by osmometer), 215.

1,3-Diformamidopropanol-2 was prepared in 95% yield by refluxing 1,3-diaminopropanol-2 and methyl formate. Isolation was the same as for VIII.

Anal. Calcd. for $C_5H_{10}N_2O_3$: N, 19.17; mol. wt., 146. Found: N, 19.29; mol. wt. (by osmometer), 142.

Ethylenebisacetamide (VII) was prepared in 11% yield by refluxing ethylenediamine with ethyl acetate. On evaporation to near dryness a crystalline product was isolated. Recrystallization was from ethyl alcohol; m.p. 172–174° lit.,[22] m.p. 175°.

Attempted Preparation of Propylenebisacetamide.—To 220 g. (2.5 moles) of ethyl acetate was added 74 g. (1.0 mole) of propylenediamine. The solution was refluxed for about 15 hr. with no change in the pot temperature. After chilling or evaporation the desired product could not be isolated. Evaporation produced an oil, the nitrogen content of which was too high for diacetylation and slightly low for monoacetylation.

1,3-Propanebisacetamide was prepared in 20% yield by refluxing 1,3-propanediamine and ethyl acetate for 20 hr. About half of the solvent was removed by distillation and the residue chilled. The white crystalline product was filtered and recrystallized from a 1:1 ethyl alcohol and acetone solution; m.p. 102–105°.

Anal. Calcd. for $C_7H_{14}N_2O_2$: C, 53.14; H, 8.92; N, 17.71; mol. wt., 158. Found: C, 52.78; H, 8.61; N, 17.69; mol. wt. (by osmometer), 158.

Bisamides from the Reaction of Diamines and Amides.—Ethylenediamine was diacylated with both formamide and acetamide by heating under reflux a slight excess of the amide with the ethylenediamine for about 5 hr. at 100–200°. Ethylenebisformamide was obtained in 72% yield by heating to 150°, although lower temperatures gave almost as high a yield. Ethylenebisacetamide was obtained in 59% yield by heating to 200°. This is the preferred synthesis of ethylenebisacetamide. Care must be taken in both of these preparations to avoid decomposition by overheating.

Methylolation of Amides and Free Formaldehyde Titration.—To each amide in Table I was added enough 20% formaldehyde (freshly prepared by heating paraformaldehyde in water at pH 8–9) to have a 50% excess of formaldehyde over that quantity required for complete methylolation. The amide generally dissolved rapidly as the mixture was placed in a water bath maintained at 60 ± 1°. Weighed portions in duplicate were removed from the solutions after 0.5 hr. and 2.5 hr. Each portion was titrated at 4° according to the procedure suggested by Morath and Woods[11] for "free formaldehyde." In this procedure the base liberated by the reaction of free formaldehyde with sodium sulfite is neutralized with excess 1 *N* hydrochloric acid. The excess acid is then back-titrated with 1 *N* sodium hydroxide. In all cases the equilibrium was established before 0.5 hr. During the 2.5-hr. reaction period the pH of the solutions decreased only slightly. A pH of 7 or higher was maintained by the solutions.

Methylolation of Ethylenebisamides for Infrared Spectra.—Ethylenebisformamide (VI) and ethylenebisacetamide (VII) were treated in alkaline solutions with two and one molar equivalents of formaldehyde, respectively. The solutions were then evaporated to dryness under vacuum at room temperature over calcium chloride. The products obtained were white solids with a slight odor of formaldehyde.

Anal. Calcd. for $C_4H_8N_2O_2{\cdot}2CH_2O$: N, 15.90. Found: N, 15.70.

Anal. Calcd. for $C_6H_{12}N_2O_2{\cdot}1CH_2O$: N, 16.08. Found: N, 16.08.

The infrared spectrum of VI had bands of interest at 3.07, 6.46, 10.19, and 11.90 μ, and no bands from 8.2–9.6 μ. The infrared spectrum of VI after methylolation had new bands of interest at 3.10, 8.01, 9.36, and 12.95 μ. The bands from VI mentioned above were not present in the spectrum of the methylolated VI.

The infrared spectrum of VII had bands of interest at 3.05, 6.40, and 10.02 μ. The infrared spectrum of VII after methylolation had new bands of interest at 3.08, 8.00, and 12.81 μ. The band from VII at 3.05 μ was still present, but was combined with the new band at 3.08 μ. The band at 6.40 μ from VII was decreased in intensity. The 10.02-μ band from VII had disappeared in the spectrum of methylolated VII. Unchanged paraformaldehyde was not present in the methylolated bisamides as indicated by absence of absorption bands of paraformaldehyde in the infrared spectra of these products.

Acknowledgment.—The authors wish to thank E. R. McCall, S. H. Miles, and G. J. Boudreaux for the spectral data, R. T. O'Connor for assistance in interpretation of these data, and L. E. Brown, A. F. Cucullu, and A. L. Alford for the analyses.

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[19] C. W. Sauer and R. J. Bruni, *J. Am. Chem. Soc.*, **77**, 2559 (1955).

[20] W. A. Noyes and D. B. Forman, *ibid.*, **55**, 3493 (1933).

[21] F. F. Blicke and C.-J. Lu, *ibid.*, **74**, 3933 (1952).

[22] A. J. Hill and S. R. Aspinall, *ibid.*, **61**, 822 (1939).