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The Synthesis and Reactions of Unsaturated N-Methylolamides[1,2,3]

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Unsaturated N-methylolamides, a new class of compounds, have been prepared. The syntheses of N-methylolmethacrylamide, N-methylolacrylamide and N,N'-bis-(methylol)-fumaramide as well as some of their derivatives are reported Upon heating, N-methylolmethacrylamide and N-methylolacrylamide have been converted to infusible polymers which are insoluble in common organic solvents. A new method of preparing N,N'-methylenebismethacrylamide and N,N'-methylenebisacrylamide has also been devised.

Unsaturated N-methylolamides such as N-methylolacrylamide (I) and N-methylolmethacrylamide (II) have been postulated as intermediates in a number of patents[4–7] in the reaction of the corresponding amides with formaldehyde leading to polymers. However, these N-methylolamides had never been isolated or identified prior to this investigation.

The preparation of II was first attempted using procedures by which saturated N-methylolamides had been successfully prepared. Following the method of Chwala,[8] methacrylamide was heated with paraformaldehyde in the presence of a catalytic amount of concentrated base. However, the amide polymerized and the paraformaldehyde was recovered. A polymer was again formed when the amide was heated in the presence of base with formalin. When this procedure[9] was modified by the addition of a small amount of powdered copper to inhibit polymerization, an oil was isolated from the reaction mixture, which polymerized on standing. This oil was found to contain some of compound II, for its ethylene chloride solution reacted with anhydrous calcium chloride upon warming to yield a calcium chloride molecular complex of II in low yield. This complex, a white crystalline, hygroscopic solid is decomposed in cold water and gives a positive test for chloride ions. No method of purification for the complex could be found. The data obtained from elementary analysis agree best with a composition of two formula weights of II and one of calcium chloride.

Compound II is obtained in crystalline form and in good yields by treating methacrylamide in dry carbon tetrachloride solution with paraformaldehyde in the presence of catalytic amounts of colloidal sodium. The success of this synthesis is primarily due to the right choice of solvent. It is well established[10] that the reaction between an amide and formaldehyde is reversible. It can, however, be forced to completion if the N-methylol compound is removed from the reaction mixture as it is formed. This is achieved by using carbon tetrachloride in which II is insoluble. Compound I is prepared by the same procedure except that ethylene chloride is used as the solvent.

Compounds I and II are stable, white crystalline solids which are readily soluble in water. They give a negative Tollens test at 25°; however, at 45° a positive test for formaldehyde is obtained. Upon heating in the presence of acids they are rapidly polymerized in aqueous solution to infusible resins. In organic solvents they are not polymerized at 25° in the presence of catalysts such as boron trifluoride etherate or methyl amyl peroxide; at 45°, however, they are converted to insoluble polymers.

N,N'-Bis-(methylol)-fumaramide (III) cannot be prepared by the method devised for the synthesis of compounds I and II because no organic solvent was found in which fumaramide is appreciably soluble. It can be prepared from formalin and fumaramide in either acidic or slightly basic solutions (*p*H 8–9). Above a *p*H value of 9, fumaramide is hydrolyzed with the evolution of ammonia. The use of acidic catalysts is preferred because better yields are obtained.

Unlike fumaramide, methacrylamide and acrylamide react with paraformaldehyde in the presence of acid catalysts to yield the corresponding N,N'-methylenebisamides. These compounds have been reported by Lundberg[11] and were synthesized from the corresponding amide and formalin in the presence of acidic catalysts. Recently[12] methylenebisacrylamide was prepared by the reaction of acrylonitrile with formaldehyde. It was found possible to prepare these compounds in somewhat better yields by a modification of the procedure used for the preparation of the N-methylolamides, substituting concentrated hydrochloric acid for colloidal sodium as the catalyst. Compounds I and II are also converted to the corresponding N,N'-methylenebisamides in the presence of catalytic amounts of acid.

The structures of the unsaturated N-methylol compounds were established by the preparation of various derivatives.

Compounds I and III react with bromine to yield the expected addition products N-methylol-2,3-dibromopropionamide (IV) and N,N'-bis-(methylol)-2,3-dibromosuccinamide (V), respectively.

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(3) Presented before the Division of Organic Chemistry at the Atlantic City Meeting of the American Chemical Society, September 18, 1952.

(4) I. G. Farbenindustrie, French Patent 827,059 (1937), and British Patent 482,897 (1938).

(5) W. Bauer, U. S. Patent 2,132,671 (1939).

(6) D. E. Strain, U. S. Patent 2,173,005 (1939).

(7) G. F. D'Alelio, U. S. Patents 2,290,674 and 2,290,675 (1943).

(8) W. Chwala, *Monatsh.*, **78**, 172 (1948).

(9) A. Einhorn, *Ann.*, **343**, 207 (1905).

(10) A. H. Lamberton, C. Lindley, P. G. Owston and J. C. Speakman, *J. Chem. Soc.*, 1641 (1949).

(11) L. Lundberg, U. S. Patent 2,475,846 (1949).

(12) E. F. Magat, *et al.*, THIS JOURNAL, **73**, 1028 (1951).

$$(R)CH{=}C(R'){-}CONHCH_2OH \xrightarrow{Br_2}$$

I, R = R' = H
III, R = CONHCH$_2$OH, R' = H

$$(R)CHBr{-}CBr(R'){-}CONHCH_2OH$$

IV, R = R' = H
V, R = CONHCH$_2$OH, R' = H

The reaction of N-methylolmethacrylamide (II) with bromine in the presence or absence of solvents takes a different course.[13] Instead of the expected N-methylol-2,3-dibromoisobutyramide, N,N'-methylenebis-(2,3-dibromoisobutyramide) (VI) is obtained. The structure of this compound is indicated by elemental analysis and by a mixed melting point determination with an authentic sample of VI which is prepared by the addition of bromine to N,N'-methylenebismethacrylamide (VII).

$$\begin{array}{l} H_2C{=}C(CH_3)CONHCH_2OH \\ \quad\text{II} \\ \qquad\qquad \xrightarrow{Br_2} (H_2CBrC(CH_3)BrCONH)_2CH_2 \\ (H_2C{=}C(CH_3)CONH)_2CH_2 \qquad\qquad \text{VI} \\ \quad\text{VII} \end{array}$$

The esterification of these N-methylol compounds was found to be extremely difficult and the esters once formed were hydrolyzed readily by water. This is at variance with the observations of Haworth[14] who reported that N-acetoxymethylphenylacetamide is not rapidly decomposed by boiling water. N,N'-Bis-(acetoxymethyl)-fumaramide is prepared by treating the corresponding methylol compound with acetyl chloride in the presence of pyridine. The acetate esters of I and II could not be prepared by this method; only water-soluble products were obtained. However, all three methylol compounds give the corresponding benzoate esters by treatment with benzoyl chloride in pyridine solution.

Treatment of a suspension of compound III in moist ether with aluminum amalgam at 25° gives the known compound N,N'-bis-(methylol)-succinamide. In aqueous solution at 50–60° reduction and demethylolation takes place and the product is succinamide. Compounds I and II polymerize in the presence of aluminum amalgam.

Experimental[15]

N-Methylolmethacrylamide (II).—Methacrylamide (42 g., 0.5 mole), paraformaldehyde (15.0 g., 0.5 mole) and 600 ml. of dry carbon tetrachloride were placed in a 500-ml. three-necked flask fitted with stirrer, thermometer and a calcium chloride drying tube. The mixture was basified with colloidal sodium dispersed in xylene[16] and was then heated to 50° for 0.5 hour. The oil which formed during this time and which was then filtered through a coarse sintered glass funnel, solidified on cooling. The product was recrystallized twice by dissolving it in warm ethyl acetate and cooling the filtered solution to −70°. A 70% yield was obtained, m.p. 53.5–54°.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.35; H, 7.76; N, 12.41.

Calcium Chloride Complex of N-Methylolmethacrylamide.—In a 500-ml. three-necked flask fitted with stirrer, thermometer and a calcium chloride drying tube were placed 21.5 g. (0.25 mole) of methacrylamide, 7.5 g. (0.25 mole) of paraformaldehyde, 200 ml. of dry ethylene chloride and 1 ml. of colloidal sodium in xylene. The temperature of the reaction mixture was maintained at 50° for 0.5 hour. A small amount of an insoluble material formed which was removed by filtration. To the clear filtrate was added 14 g. (0.12 mole) of anhydrous calcium chloride and the suspension was vigorously stirred for 24 hours. After filtration and drying, the complex was obtained as a crystalline product, m.p. 155°, yield 92%.

Anal. Calcd. for $C_{10}H_{18}N_2O_4CaCl_2$: C, 35.16; H, 5.28; Ca, 11.72. Found: C, 38.0; H, 5.72; Ca, 10.2.

N-Methylolacrylamide (I).[17]—The same experimental procedure was followed as in the preparation of N-methylolmethacrylamide except that dry ethylene chloride was used as the solvent. The yield of the product was 70%, m.p. 74–75°.

Anal. Calcd. for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.86. Found: C, 47.47; H, 6.84; N, 13.91.

N,N'-Bis-(methylol)-fumaramide (III). (a) Basic Catalysis.—Fumaramide (17.2 g., 0.15 mole) was added to 48.6 g. (0.30 mole) of 37% formalin solution, and the *p*H of the suspension was adjusted to 8–9 by the dropwise addition of a base such as concentrated ammonium hydroxide. This *p*H was maintained by the periodic addition of base while the mixture was heated at 90–95° for 0.5 hour. Because all of the amide had not dissolved at the end of this time, an additional 32 ml. of formalin and 32 ml. of water were added, and the *p*H was again adjusted to 8–9. After heating the mixture for an additional ten minutes, all of the amide dissolved. Upon cooling, a white solid precipitated which was recrystallized from boiling water. The product obtained with 49% yield, did not melt below 360°, but slowly charred above 270°.

(b) **Acid Catalysis.**—To 80 ml. of water containing about 1 ml. of concentrated hydrochloric acid were added 13.2 g. (0.12 mole) of fumaramide and 22 g. (0.27 mole) of 37% formalin solution. The suspension was boiled for 1.5 hours, after which time all the amide had dissolved and a small amount of an amorphous solid appeared which was filtered off through a preheated coarse sintered glass filter. Cooling of the filtrate gave 63% of product.

Anal. Calcd. for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.35; H, 5.83; N, 15.82.

N,N'-Methylenebisacrylamide. (a) With N-Methylolacrylamide.—N-Methylolacrylamide (4.04 g., 0.04 mole) was added to 30 ml. of ethylene chloride along with three drops of concentrated hydrochloric acid. The mixture was refluxed until all the oil had dissolved, which required 30 minutes. An amorphous solid (0.57 g.) was filtered from the hot solution. Upon evaporating the filtrate to one-third of its volume and cooling, 2.16 g. (67% yield) of N,N'-methylenebisacrylamide, m.p. 181–182°, lit. value[11] 184–185°, crystallized from solution. A mixed melting point with an authentic sample was found to be 182°.

(b) **With Acrylamide.**—In a 100-ml. round-bottom flask fitted with a reflux condenser, were placed 7.1 g. (0.10 mole) of acrylamide, 1.5 g. of paraformaldehyde (0.05 mole CH_2O), 30 ml. of ethylene chloride and three drops of concentrated hydrochloric acid. The mixture was heated for 20 minutes at reflux, after which time a solid began to crystallize from the previously clear solution. Cooling yielded 6.60 g. of product and an additional 1 g. of crystals was obtained on evaporating the mother liquor to one-third of its original volume. The total yield was 89%, m.p. 181–182°.

N,N'-Methylenebismethacrylamide (VII). (a) With Methacrylamide.—The experimental procedure was the same as for the preparation of N,N'-methylenebisacrylamide. A 70% yield of product was obtained, m.p. 160–161°, lit. value[11] 164–165°. A mixed melting point with an authentic sample was found to be 163°. The melting point of this material should be taken by inserting the sample in the heating bath just a few degrees below its melting point, otherwise the compound will polymerize without melting.

(b) **With N-Methylolmethacrylamide.**—To 20 ml. of ethylene chloride containing two drops of concentrated hydrochloric acid were added 2.30 g. (0.02 mole) of N-methylolmethacrylamide and 1.6 g. (0.02 mole) of methacrylamide; the mixture was refluxed for 30 minutes. The hot solution

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[13] This reaction is being currently investigated and will be discussed in a forthcoming publication.

[14] R. D. Haworth, D. H. Peacock, W. R. Smith and R. MacGillivary, *J. Chem. Soc.*, 2974 (1952).

[15] All melting points are uncorrected.

[16] Ordinary sodium, sodium amide or sodium ethoxide can also be employed.

[17] N-Methylolacrylamide did not form a complex with anhydrous calcium chloride.

was filtered and 0.17 g. of an amorphous solid was retained. Cooling of the filtrate and evaporation of the mother liquor gave a total of 3 g. (80% yield), of product, m.p. 162–163°.

N,N′-Methylenebismethacrylamide was also obtained in 67% yield by heating N-methylolmethacrylamide in the presence of a catalytic amount of concentrated hydrochloric acid.

N-Methylol-2,3-dibromopropionamide (IV).—Bromine was added dropwise with cooling to 1 g. (0.01 mole) of N-methylolacrylamide dissolved in carbon tetrachloride, until the color of bromine remained. Upon cooling, 2.5 g. (96%) of product was obtained which after recrystallization from aqueous ethanol melted at 161–162°.

Anal. Calcd. for $C_4H_7NO_2Br_2$: C, 18.39; H, 2.68; N, 5.36; Br, 61.30. Found: C, 18.46; H, 2.70; N, 5.17; Br, 61.0.

N,N′-Bis-(methylol)-2,3-dibromosuccinamide (V).—N,N′-Bis-(methylol)-fumaramide (1.86 g., 0.01 mole) was dissolved in 15 ml. of hot water, and 1.66 g. (0.02 mole) of bromine was added. The mixture was stirred until the color of bromine had almost disappeared. From the cooled solution, 1.3 g. (27%) of the adduct precipitated. It was recrystallized several times from boiling water. The compound did not melt but charred above 250°.

Anal. Calcd. for $C_6H_{10}N_2O_4Br_2$: C, 21.55; H, 2.96; N, 8.38. Found: C, 21.0; H, 2.83; N, 8.51.

N,N′-Methylenebis-(2,3-dibromoisobutyramide) (VI). (a) With N,N′-Methylenebismethacrylamide.—To 0.22 g. (1.2 mmoles) of N,N′-methylenebismethacrylamide was added a solution of bromine in CCl_4 until the color of the bromine remained. The reaction mixture was gently warmed to remove the excess bromine, and upon cooling 0.58 g. (88%) of product was obtained. After recrystallization from absolute ethanol, 0.40 g. of needle-like crystals, m.p. 206–206.5°, was isolated.

Anal. Calcd. for $C_9H_{14}N_2O_2Br_4$: C, 21.51; H, 2.78; N, 5.57. Found: C, 21.58; H, 2.85; N, 5.42.

(b) **With N-Methylolmethacrylamide.**—In 5 ml. of dry ethylene chloride was dissolved 0.58 g. (5.0 mmoles) of N-methylolmethacrylamide. The solution was cooled in an ice-bath and liquid bromine was added dropwise until the color of the bromine remained. The solvent was then evaporated in an air stream, and the semi-solid residue was crystallized from absolute ethanol, yielding 0.80 g. (40%) of N,N′-methylenebis-(2,3-dibromoisobutyramide), m.p. 204–205°. A mixed melting point determination with an authentic sample was found to be 205°.

N-Benzoxymethacrylamide.—N-Methylolacrylamide (10 g., 0.09 mole) was dissolved in 50 ml. of pyridine, and 14.3 g. (0.10 mole) of benzoyl chloride was added dropwise with cooling. The reaction mixture was allowed to stand at 25° for 0.5 hour before being poured into ice-water. The insoluble solid obtained weighed 14.5 g. (73%) and melted at 104–106°. After recrystallization from 30% aqueous ethanol the m.p. was raised to 110.5°.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.39; H, 5.42; N, 6.84.

N-Benzoxymethylmethacrylamide.—The experimental procedure was the same as for the preparation of N-benzoxymethylacrylamide. The ester was recrystallized from petroleum ether. The yield was 48%, m.p. 88.5–89°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 5.84; N, 6.35.

N,N′-Bis-(benzoxymethyl)-fumaramide.—The procedure for the preparation of N-benzoxymethylacrylamide was followed. Recrystallization from nitromethane gave the ester in a yield of 54%, m.p. 224° dec. To observe this melting point, it is necessary to insert the sample just below 224°.

Anal. Calcd. for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.92; H, 4.87; N, 7.38.

N,N′-Bis-(acetoxymethyl)-fumaramide.—To 1 g. (5.7 mmoles) of N,N′-bis-(methylol)-fumaramide suspended in 10 ml. of pyridine was slowly added 1.0 g. (13 mmoles) of acetyl chloride. An exothermic reaction occurred and the methylol compound dissolved slowly. The reaction mixture was then allowed to stand at 25° for 0.5 hour before being poured into ice-water. A 50% yield of the ester was obtained for which no suitable solvent for recrystallization could be found. The ester did not melt up to 360°.

Anal. Calcd. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.22; H, 5.45; N, 11.01.

Reduction of N,N′-Bis-(methylol)-fumaramide. (a) With Wet Ether.—N,N′-Bis-(methylol)-fumaramide (0.15 g., 0.7 mmole) was suspended in 100 ml. of diethyl ether containing a few drops of water.

Aluminum amalgam was prepared as follows: 3 g. of granulated aluminum was washed with a 10% sodium hydroxide solution until hydrogen was evolved vigorously. The metal was thoroughly washed with distilled water and then treated for five seconds with a 1% solution of mercuric chloride. The amalgam was then washed with distilled water, ethanol and finally with ether.

Without exposure to the air, the amalgam was transferred to the reaction vessel containing the ethereal suspension of the methylol derivative and the mixture was allowed to stand at 25° for 24 hours. The ether was then allowed to evaporate, and the residue was extracted with boiling ethanol. Evaporation of the solvent left 80 mg. of a white solid which melted at 145–165°. Recrystallization from hot water raised the melting point to 165–167°. N,N′-Bis-(methylol)-succinamide has been reported[9] to melt at 167°.

(b) **With Water.**—Ten grams of aluminum amalgam was placed in 25 ml. of distilled water. One gram (5.7 mmoles) of N,N′-bis-(methylol)-fumaramide was added and the mixture was heated at 50–60° for five hours. Extraction of the dry residue with boiling ethanol and evaporation of the solvent gave 0.15 g. of product which after recrystallization from hot water melted at 251–252°. A mixed melting point determination with an authentic sample of succinamide was 250–252°.

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