

Synthetic Biologically Active Polymers. VI. Sulfonamide- and Sulfone-Dimethylolurea Copolymers

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Synopsis

Dimethylolurea was found to copolymerize with a number of sulfonamides and sulfones (Ia-h) to yield oligomeric condensation products (IIa-h). The preparation and characterization studies relevant to these materials are described. Products IIc, IIe, IIg, and IIh were active as antimalarial drugs.

INTRODUCTION

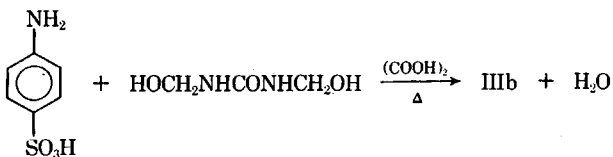
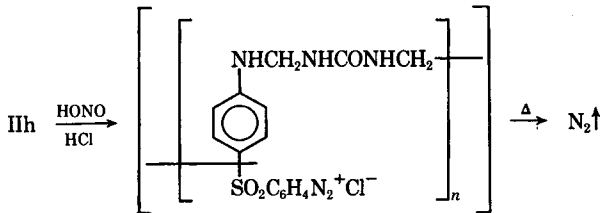
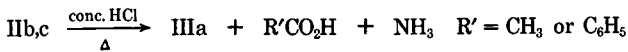
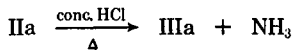
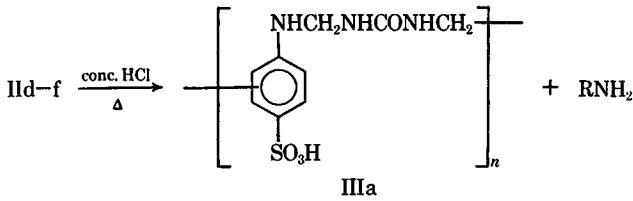
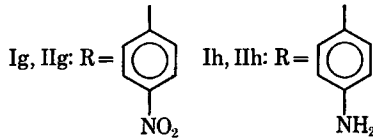
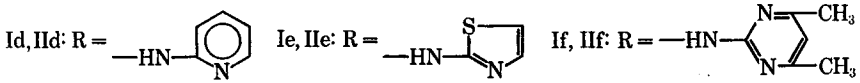
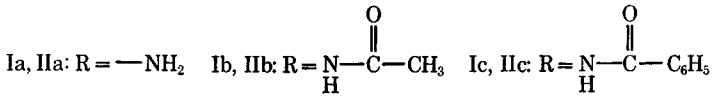
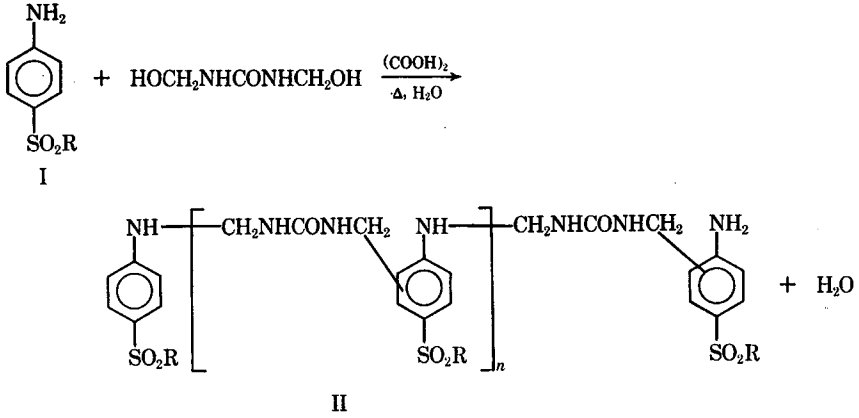
In order to observe the effect of polymerization on the activity of drugs, we have undertaken a series of investigations aimed at copolymerizing drugs with various comonomers.¹⁻⁵ We have previously reported on the synthesis and properties of several sulfonamide-formaldehyde copolymers³⁻⁵ This report is concerned with the preparation of several novel sulfonamide-dimethylolurea copolymers (IIa-f). Since aminodiphenylsulfones might be considered as sulfonamide vinylogues, the results obtained from copolymerization of two sulfones (Ig, h) with dimethylolurea also are reported herein. These compounds, to our knowledge, represent new classes of copolymers. The only reaction in the literature concerning the copolymerization of primary arylamines with dimethylolurea described the copolymerization of aniline with dimethylolurea, but no structural evidence concerning the reaction product was presented.⁶

RESULTS AND DISCUSSION

The copolymerization of certain sulfonamides (Ia-f) and sulfones (Ig, h) with dimethylolurea was carried out in a refluxing aqueous acidic medium. These reactions are depicted below, and some physical data relevant to these materials is shown in the experimental section.

The data indicate that the reaction products are oligomeric. The calculated elemental analyses based on the observed average molecular weights were not wholly consistent for a 1:1 copolymer. Noting this, it was de-

Scheme I



ecided that before any structural conclusions could be drawn, more data were needed.

The infrared spectra as well as the elemental analyses of IIa-h were consistent with the fact that the products contained moieties which were derived from both comonomers.

It seemed to us that hydrolysis of IIa-f should yield copolymers related to IIIa. Further, it also seemed possible that IIIb which should be structurally similar to IIIa could be synthesized independently. Thus, when dimethylolurea was condensed with sulfanilic acid, a buff-colored product was obtained (IIIb). The average molecular weight of IIIb was 1710, with an average degree of polymerization (d.p.) of 5. The elemental analyses, within the limits of error inherent in these systems, was consistent with these facts, and the infrared spectrum was comparable with that of IIIa obtained by subsequent hydrolysis of IIa-f. The products (IIIa, b) showed strong infrared adsorption bands, typical of sulfonic acids, at 1033 cm^{-1} . For example, IIa was refluxed with concentrated hydrochloric acid. Ammonia was detected and a light-brown powder (IIIa) was collected which had a softening temperature of 265° - 270°C and an intrinsic viscosity of 0.075 dl/g at 25°C in dimethylsulfoxide (DMSO). The average molecular weight of IIIa was 3400. This corresponds to an average d.p. of 10. Before hydrolysis, IIa had an average molecular weight of 3030 and a d.p. of 10; thus, total cleavage of the polymer backbone did not occur and the hydrolysis was relatively selective in that the chain mer structure remained apparently intact.

When IIc was hydrolyzed, benzoic acid, ammonia, and a buff-colored residue (IIIa) having an average molecular weight of 1025 were formed. This corresponds to a d.p. of 2 and was consistent with the d.p. of 2 found for IIc.

The hydrolysis study of IIa-f demonstrates that the copolymer backbone is to some extent stable to the very stringent hydrolysis conditions and that condensation of dimethylolurea with sulfonamides probably involves the N^4 -nitrogen. The latter conjecture is supported by the comparability of IIIa, obtained by the hydrolysis of IIa-f, and IIIb, for which no N^4 -hydrogen was present for possible condensation.

Hydrolyses were carried out on all the sulfonamide-dimethylolurea copolymers. In each case, IIIa was isolated and found to correspond with IIIb. However, some of the basic amino cleavage products were not isolable due to the stringent reaction conditions. Acid sensitive groups such as 2-aminothiazole and the pyrimidine derived from sulfamethazine apparently decomposed, and ammonia gas was formed. For example, 2-amino-4,6-dimethylpyrimidine could not be isolated from the reaction mixture when IIIf was refluxed for 20 hr in concentrated hydrochloric acid. However, by decreasing the reaction time to 1 hr, a 2% yield of the pyrimidine was obtained. With the short reflux time, incomplete hydrolysis was evident when the polymeric product showed only a weak sulfonic acid band at 1033 cm^{-1} . Similarly, 2-aminothiazole could not be isolated from the hy-

drolysis of IIe for 20 hr. However, hydrolysis for 1 hr yielded 5% of 2-aminothiazole and incompletely hydrolyzed IIe.

Further evidence for the sensitivity of the thiazole and the pyrimidine to the acid hydrolysis reaction was obtained by another method. A known quantity of each amine was subjected to hydrolysis conditions identical to those used for the polymers. After various time intervals, the quantity of amine recovered from the reaction was noted. For example, the recovery of 2-amino-4,6-dimethylpyrimidine after 1 hr of hydrolysis was 7%. However, after 2 hr, the recovery was 0%. This reasonably supports the findings that 2-amino-4,6-dimethylpyrimidine was not isolable when IIc was refluxed for 20 hr in aqueous hydrochloric acid. Recovery of 2-aminothiazole after 1 hr of hydrolysis was 5%, but after 2 hr none was recovered.

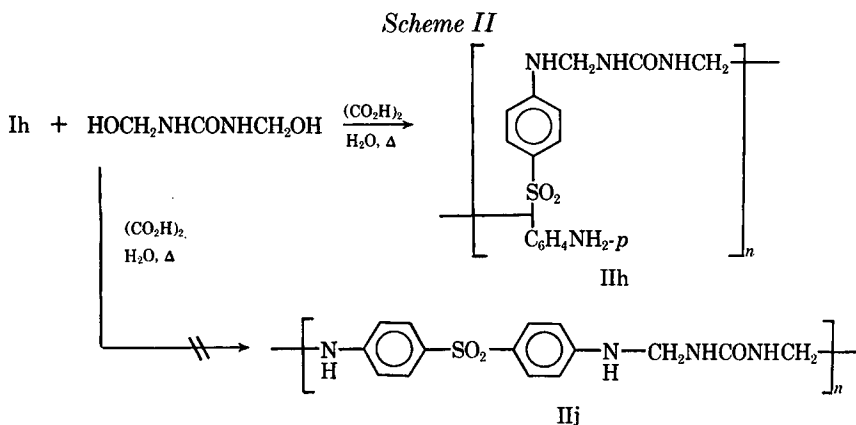
Two sulfones, Ig and Ih, with condensable amino groups, were reacted with dimethylolurea under the same acidic conditions previously cited for Ia-f.

When Ig was reacted with dimethylolurea, IIg having an intrinsic viscosity of 0.034 dl/g at 25°C in dimethylsulfoxide was obtained. The molecular weight, obtained by light scattering, was 1190. This corresponds to an average d.p. of 4.

IIg showed a strong absorption band, typical of aryl sulfones, at 1150 cm^{-1} . The copolymer also exhibited a strong carbonyl absorption at 1620 cm^{-1} , arising from the carbonyl group of copolymerized dimethylolurea. This band was not present in the spectrum of Ig. Generally, the infrared spectrum was comparable with the assigned polymer structure.

Product Ih has two equivalent amine groups available for condensation with dimethylolurea. Thus, polycondensation could occur at one or both amino groups to give one of two different polymers or a mixture of the two, as reported in similar copolymerization processes.⁵ A diazotization experiment previously designed⁵ to test for an analogous structure ambiguity was employed here (see schemes I and II). At ambient temperature, the diazonium salt decomposed with subsequent evolution of nitrogen. The volume of nitrogen evolved was measured. The presence of one free amine group per mer unit subject to error limits of $\pm 6\%$ was indicated. The average molecular weight of IIh was 1925. This corresponds to a d.p. of 5. The elemental analysis of the copolymer indicated a d.p. of 5, and the infrared spectrum was consistent with the assigned structure (IIh). Thus, structure IIh seems more probable than IIj.

The elemental analyses of IIa-h were found to be generally consistent with the calculated values, based on the respective degree of polymerization. However, it should be noted that the analyses did not agree exactly with the calculated values. The calculated values were determined by measuring the average molecular weight of each polymer. This method inherently yields information for an average-size molecule in the sample, whereas the copolymer is usually composed of a distribution of molecules of various molecular weights. This fact, along with some uncertainty as to actual polymer endgroups, might reasonably account for the differences between the



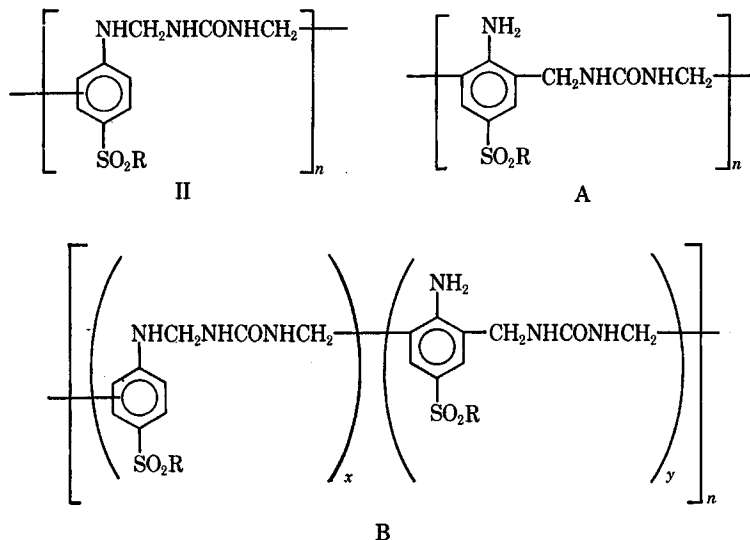
observed and calculated analyses. Tentatively, we have chosen to formulate the copolymer structures as II.

Although the generalized *average* structure for the copolymer as shown in scheme I is depicted as II, it should be pointed out that this structure merely represents the best one that can be written on the basis of the data in hand. Characterization of copolymers wherein the comonomers have large molecular weights can be a difficult task because the endgroups exert a very large effect on elemental analyses, particularly where the degree of polymerization is low and the copolymer is polydisperse. In the cases described herein, even where the degree of polymerization was the largest (IIa), the carbon, hydrogen, nitrogen, and sulfur analyses vary widely, particularly the sulfur analyses. If one calculates the copolymer elemental analyses for various alternating combinations, it is found that, depending on the nature of the endgroups and the assumed degree of polymerization, the calculated percentages of sulfur vary as much as 5% for the same copolymer, nitrogen percentages vary up to 3%, and hydrogen percentages vary up to 0.4–0.5%. In addition, since the calculated elemental percentage values for a given copolymer ought to be based on the observed *average* molecular weight, and the molecular weight determinations have an error of $\pm 7\%$, this too results in calculated elemental percentages that vary over a considerable range.

The *suggested* general polymer structure, II, was postulated because the observed sulfur analyses were high and the observed nitrogen analyses were low in comparison to those calculated employing the observed molecular weights or using assumed alternating inclusion of the monomers into the copolymers. This suggested that for the average copolymer molecule, both endgroups were derived from the sulfonamide comonomers. These calculated values are set forth in the experimental section and no matter what other method of calculation was used, these values were closest to those actually observed.

Another problem associated with guessing that the average general structure was that of II was how to determine the nature of the bonding sites linking the sulfonamide and dimethylolurea units which comprise the copolymer; and there are several possibilities, as shown in scheme III:

Scheme III



Since structures A and B possess primary amino groups characteristic of the copolymerization process, if we had at hand a method for the detection of primary amino groups, we might be able to get some idea about the nature of the bonding. We decided to react each copolymer with nitrous acid and measure the quantity of nitrogen evolved. If the copolymer structures were exactly as indicated in structure II, then the quantity of nitrogen released would be equal only to that liberated from other diazotizable groups in the copolymer structure that were not involved in the polymerization process. In each case, the results of the diazotization experiments showed that, within the experimental error of 6%, the average polymer molecule had one primary amino group in addition to diazotizable groups not related to the bonds involved in copolymer formation. Prior to diazotization of the copolymers, the sulfonamide monomers were also treated with nitrous acid to see how quantitative the reaction was. Within the limits of $\pm 6\%$, each monomeric sulfonamide yielded the calculated quantity of nitrogen. The equation typifying these reactions is exemplified in scheme I by the reaction of IIh with nitrous acid. Therefore, it seems reasonable to assume that condensation polymerization took place mainly on the N⁴-nitrogen and the aromatic ring to yield a structure more similar to II than other possible structures related to A or B. But since we can only speak of average structures, it is also possible that a few primary amino groups similar to those depicted in structures A and B may be present.

Another factor which also might bear on the low nitrogen and high sulfur content is the possibility of hydrolysis of the group on the N⁴-nitrogen atom to yield sulfonic acid groups in the copolymer. However, we have found that this is negligible under the mildly acidic polymerization conditions. Such hydrolyses only occur readily when strong mineral acids are present,

as shown in scheme I for the hydrolysis reactions. Moreover, none of the copolymers II show the band typical of sulfonic acids at 1033 cm^{-1} in their infrared spectra.

For the reasons cited above, we have chosen to exemplify the structures of the copolymers as II. But even in the light of the evidence presented, it is unlikely that this structure is an exact representation, for it must again be emphasized that we are speaking only of average structures. Nevertheless, in spite of the fact that a structure for II cannot really be assigned with absolute certainty, the product compositions are constant and reproducible, as are the associated physical and chemical properties.

Antimalarial screening data obtained using mice showed that copolymers II_d, II_f, II_g, and II_h had curative properties of about the same magnitude as the monomeric sulfonamides at the same dose levels. Monomer I_h showed toxicity at the higher dose levels, but polymer II_h did not. Copolymers II_a, II_b, II_c, and II_e were inactive as antimalarials.

EXPERIMENTAL

All calculated analyses values below are based on observed copolymer molecular weights. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Nomenclature for interpretation of infrared data: s = strong absorbance, m = medium absorbance, and w = weak absorbance. All infrared spectra were run with potassium bromide pellets. Viscosity measurements were obtained with an Ostwald No. 50 viscometer (reproducibility $\pm 3\%$) at $25^\circ \pm 0.05^\circ$ using DMSO as solvent. Intrinsic viscosities were determined in the usual manner. All molecular weight determinations were performed with a Brice Phoenix Model 2000 light-scattering photometer. DMSO was used as the polymer solvent.

Sulfanilamide-Dimethylolurea Copolymer (II_a). Water (150 ml), 5.16 g (0.03 mole) sulfanilamide, and 0.90 g (0.01 mole) oxalic acid were stirred and heated to reflux. To the hot solution was added 3.60 g (0.03 mole) dimethylolurea. Within 1 hr, a gummy white-colored resin formed on the walls of the flask. After refluxing for 8 hr, the solution was allowed to cool and the supernatant decanted. The resin was collected, dried, powdered, washed in boiling water three times, and continuously extracted with methanol for 24 hr. The yield was 3.90 g. The copolymer had a softening temperature of $185^\circ\text{--}190^\circ\text{C}$.

ANAL. Calcd for $\text{C}_{105}\text{H}_{139}\text{N}_{46}\text{O}_{35}\text{S}_{12}$: C, 42.25%; H, 4.65%; N, 21.05%; S, 12.85%. Found: C, 42.50%; H, 4.82%; N, 19.28%; S, 14.70%.

INFRARED DATA (cm^{-1}). 750w, 810m, 900m, 1070m, 1130s, 1275s, 1450m, 1560s, 1600s, 2950s, 3200s.

VISCOSITY. $[\eta] = 0.053\text{ dl/g}$ at 25°C in DMSO as solvent.

MOLECULAR WEIGHT. $M_w = 3030 \pm 7\%$.

Hydrolysis of II_a. Two grams of the sulfanilamide-dimethylolurea copolymer (II_a) was dissolved in 10 ml concentrated hydrochloric acid, and the solution was refluxed for 20 hr. The solution was made basic with 25%

aqueous sodium hydroxide, and a strong odor of ammonia was noted. The solution was acidified and evaporated to dryness. The light-buff-colored residue was thoroughly washed with water to remove salts. The product (0.65 g) had a softening temperature of 265–270°C and did not decompose up to 300°C. The material gave an infrared spectrum comparable to that of the copolymer of sulfanilic acid–dimethylolurea (IIIb).

INFRARED DATA (cm^{-1}). 765w, 830w, 880w, 945m, 1033m, 1150s, 1325s, 1450m, 1610m, 2800m, 3200s.

MOLECULAR WEIGHT. $\bar{M}_w = 3400 \pm 7\%$.

Sulfacetamide–Dimethylolurea Copolymer (IIb). Sulfacetamide (4.28 g, 0.02 mole) in 150 ml water and acidified with oxalic acid (0.45 g, 0.005 mole) was stirred and heated to reflux. To this solution, 2.40 g (0.02 mole) dimethylolurea was added. After the first hour of reflux, the solution was a clear-yellow color. The mixture was refluxed for an additional 4 hr and allowed to cool. A bright-yellow resin soon deposited on the walls of the flask. The supernatant was decanted and the gum was collected and dried at 110°C. The brittle polymer was powdered, washed three times with hot water, and extracted for 24 hr with methanol. The yield was 2.15 g. The copolymer had a softening temperature of 165–170°C.

ANAL. Calcd for $\text{C}_{41}\text{H}_{52}\text{N}_{14}\text{O}_{13}\text{S}_4$: C, 44.40%; H, 4.68%; N, 17.70%; S, 11.55%. Found: C, 44.40%; H, 4.79%; N, 14.90%; S, 14.55%.

INFRARED DATA (cm^{-1}). 830m, 935w, 985w, 1075s, 1125s, 1200w, 1300m, 1410m, 1460m, 1550s, 1675s, 2700m, 3200s.

VISCOSITY. $[\eta]$ 0.041 dl/g at 25°C in DMSO as solvent.

MOLECULAR WEIGHT. $\bar{M}_w = 1190 \pm 7\%$.

Hydrolysis of IIb. Two grams of the sulfacetamide–dimethylolurea copolymer was dissolved in 10 ml concentrated hydrochloric acid, and the solution was refluxed for 20 hr. The solution was made basic with 25% aqueous sodium hydroxide, and a very strong odor of ammonia was detected. The solution was acidified with hydrochloric acid and evaporated to dryness. During the evaporation process, the odor of acetic acid was noted. A light-brown powder (0.20 g) which did not soften or melt below 300°C remained. This product showed a strong absorption band, typical of sulfonic acids at 1033 cm^{-1} , and the spectrum was comparable with that of IIIb.

INFRARED DATA (cm^{-1}). 820w, 880w, 1033s, 1370m, 1450m, 1550m, 1600m, 2800m, 3200m.

MOLECULAR WEIGHT. $\bar{M}_w = 1050 \pm 7\%$.

Sulfabenzamide–Dimethylolurea Copolymer (IIc). Five and five tenths grams (0.02 mole) sulfabenzamide was added to 150 ml water. The mixture was acidified with oxalic acid (0.45 g, 0.005 mole), heated to reflux, and 2.40 g (0.02 mole) dimethylolurea was added. After the first hour of reflux, a light-yellow resin formed on the walls of the flask. The reaction mixture was refluxed for an additional 5 hr. The warm supernatant was then decanted and the polymer was collected, dried, powdered, and washed several

times in boiling water. After subsequent extraction with methanol for 24 hr, the polymer yield was 3.00 g. The copolymer had a softening temperature of 165–170°C.

ANAL. Calcd for $C_{61}H_{59}N_{14}O_{19}S_4$: C, 53.89%; H, 4.43%; N, 14.45%; S, 9.44%. Found: C, 53.25%; H, 4.70%; N, 13.10%; S, 9.88%.

INFRARED DATA (cm^{-1}). 710m, 830s, 890m, 1150s, 1240s, 1350s, 1420m, 1460m, 1500m, 1600s, 1625s, 3200s.

VISCOSITY. $[\eta] = 0.040$ dl/g at 25° in DMSO as solvent.

MOLECULAR WEIGHT. $\bar{M}_w = 1400 \pm 7\%$.

Hydrolysis of IIc. Two grams of the sulfabenzamide–dimethylolurea copolymer was dissolved in 10 ml concentrated hydrochloric acid and the solution was refluxed for 20 hr. The solution was allowed to cool and made basic with 25% aqueous sodium hydroxide. A strong odor of ammonia was detected. A white crystalline deposit (0.46 g, 67%) in the condenser was collected and identified as benzoic acid (mp 123°C; literature mp 122°C) by infrared comparison with an authentic sample. The solution was reacidified with hydrochloric acid and evaporated to dryness. The brown residue was thoroughly washed with water to remove salts. The product (1.00 g), which was heat stable up to 300°, gave an infrared spectrum comparable to IIIb.

INFRARED DATA (cm^{-1}). 830w, 930w, 1033s, 1110m, 1280s, 1310m, 1450m, 1550m, 1600m, 2800m, 3000s.

MOLECULAR WEIGHT. $\bar{M}_w = 1025 \pm 7\%$.

Sulfapyridine–Dimethylolurea Copolymer (IIId). A solution of 4.92 g (0.02 mole) sulfapyridine and 0.45 g (0.005 mole) oxalic acid in 150 ml water was heated to reflux, and 2.40 g (0.02 mole) dimethylolurea was added. Within $\frac{1}{2}$ hr, a light-yellow resin deposited on the walls of the flask. The reaction was refluxed for an additional 5 hr. The warm supernatant was decanted and the polymer was collected, dried, powdered, washed three times in hot water, and extracted with methanol for 24 hr. The polymer yield was 3.00 g. The material had a softening temperature of 153–155°C.

ANAL. Calcd for $C_{81}H_{81}N_{26}O_{17}S_6$: C, 50.75%; H, 4.45%; N, 20.50%; S, 10.10%. Found: C, 51.60%; H, 4.59%; N, 16.85%; S, 11.12%.

INFRARED DATA (cm^{-1}). 760m, 820w, 940m, 1000m, 1075s, 1140s, 1230m, 1350s, 1460s, 1575s, 1610s, 2650m, 3200m.

VISCOSITY. $[\eta] = 0.035$ dl/g at 25° in DMSO as solvent.

MOLECULAR WEIGHT. $\bar{M}_w = 1175 \pm 7\%$.

Hydrolysis of IIId. Two grams of the sulfapyridine–dimethylolurea copolymer was dissolved in 10 ml of concentrated hydrochloric acid, and the solution was refluxed for 20 hr. The solution was then made basic with 25% aqueous sodium hydroxide. The solution was extracted with four 25-ml portions of ether. The combined extracts were dried ($MgSO_4$), and the solvent was removed to leave a residue of 0.47 g (73%) 2-aminopyridine which was identical in all respects with an authentic sample. The basic aqueous phase was acidified and evaporated to dryness. The resi-

due was thoroughly washed with water to remove salts. A brown powder (1.00 g) which did not soften or melt below 300°C remained. This material gave an infrared spectrum nearly identical to that of the copolymer of sulfanilic acid-dimethylolurea (IIIb).

INFRARED DATA (cm^{-1}). 680w, 820m, 880w, 1033s, 1100w, 1150s, 1210m, 1350w, 1450m, 1550m, 1610m, 2800m, 3200s.

MOLECULAR WEIGHT. $\bar{M}_w = 1010 \pm 7\%$.

Sulfathiazole-Dimethylolurea Copolymer (IIe). Water (150 ml), 4.86 g (0.02 mole) sulfathiazole, and 0.45 g (0.005 mole) oxalic acid were heated to reflux. To the hot solution was added 2.40 g (0.02 mole) dimethylolurea. Reflux was sustained for 5 hr after which time the precipitated white polymer was recovered by filtration. The product was washed three times in hot water and extracted for 24 hr with methanol. The yield was 5.40 g. Upon heating, the polymer changed from white to a brown color at 270°C, but did not soften or melt below 300°C.

ANAL. Calcd for $\text{C}_{69}\text{H}_{76}\text{N}_{28}\text{O}_{17}\text{S}_{12}$: C, 42.50%; H, 3.80%; N, 20.10%; S, 13.95%. Found: C, 42.09%; H, 4.32%; N, 17.40%; S, 10.22%.

INFRARED DATA (cm^{-1}). 690s, 800m, 830m, 915s, 1075s, 1100s, 1170s, 1250s, 1300m, 1360w, 1450s, 1550s, 2800m, 3200m.

VISCOSITY. $[\eta] = 0.046$ dl/g at 25° in DMSO as solvent.

MOLECULAR WEIGHT. $\bar{M}_w = 1870 \pm 7\%$.

Hydrolysis of IIe. Two grams of the sulfathiazole-dimethylolurea copolymer was dissolved in 10 ml concentrated hydrochloric acid, and the solution was refluxed for 20 hr. When the solution was made basic with 25% aqueous sodium hydroxide, a strong odor of ammonia was detected. The solution was extracted with four 25-ml portions of ether. The combined extracts were dried (MgSO_4), and the solvent was evaporated. None of the expected 2-aminothiazole was recovered. The basic aqueous phase was acidified and evaporated to dryness. The residue was thoroughly washed with water to remove salts. The product (1.00 g) which was heat stable up to 300°C, gave an infrared spectrum nearly identical to that of the copolymer of sulfanilic acid-dimethylolurea (IIIb).

INFRARED DATA (cm^{-1}). 690w, 750m, 820m, 890m, 1033s, 1150s, 1260m, 1370m, 1400w, 1550m, 1610s, 2800m, 3200m.

Sulfamethazine-Dimethylolurea Copolymer (IIIf). A solution containing 5.56 g (0.02 mole) sulfamethazine and 0.45 g (0.005 mole) oxalic acid in 150 ml water was heated to reflux. To the hot solution was added 2.40 g (0.02 mole) dimethylolurea. After 1 hr of reaction, a yellow resin formed on the sides of the flask. Reflux was continued for 5 additional hours. The polymer was recovered by decanting the hot supernatant. The resin was dried, powdered, washed several times with hot water, and extracted for 24 hr with methanol. The yield was 5.50 g. The copolymer had a softening temperature of 190-195°C.

ANAL. Calcd for $\text{C}_{37}\text{H}_{104}\text{N}_{37}\text{O}_{17}\text{S}_6$: C, 50.00%; H, 4.97%; N, 22.70%; S, 9.20%. Found: C, 50.54%; H, 4.54%; N, 19.60%; S, 9.75%.

INFRARED DATA (cm^{-1}). 785w, 850m, 965 w, 1075s, 1140s, 1280w, 1320w, 1360s, 1500m, 1560s, 3100s.

VISCOSITY. $[\eta] = 0.049$ dl/g at 25° in DMSO as solvent.

MOLECULAR WEIGHT. $\bar{M}_w = 2250 \pm 7\%$.

Hydrolysis of III. Two grams of the sulfamethazine-dimethylolurea copolymer was dissolved in 10 ml concentrated hydrochloric acid, and the solution was refluxed for 20 hr. When the solution was made basic with 25% aqueous sodium hydroxide, a strong odor of ammonia was detected. The solution was extracted with four 25-ml portions of ether. The combined extracts were dried (MgSO_4), and the solvent was evaporated. None of the expected 2-amino-4,6-dimethylpyrimidine was recovered. The basic aqueous phase was acidified and evaporated to dryness. The residue was thoroughly washed with water to remove salts. The product (0.95 g) gave an infrared spectrum comparable to that of IIIb.

INFRARED DATA (cm^{-1}). 690m, 770w, 830w, 870w, 950m, 1033s, 1100s, 1160s, 1310m, 1370m, 1450m, 1550w, 1620s, 2800m, 3200m.

4-Amino-4'-Nitrodiphenylsulfone-Dimethylolurea Copolymer (IIg)

A mixture of 4-amino-4'-nitrodiphenylsulfone (5.56 g, 0.02 mole) and oxalic acid (0.45 g, 0.005 mole) in 150 ml water was heated to reflux. Dimethylolurea (2.40 g, 0.02 mole) was then added to the hot reaction mixture. Within $\frac{1}{2}$ hr, a light brown resin formed in the flask. The polymer was collected by filtration and washed three times in hot water and continuously extracted with methanol for 24 hours. The yield was 3.50 g. The copolymer had a softening temperature of 143–145°.

ANAL. Calcd for $\text{C}_{117}\text{H}_{108}\text{N}_{30}\text{O}_{39}\text{S}_8$: C, 50.00%; H, 3.83%; N, 15.00%; S, 9.14%. Found: C, 52.08%; H, 3.61%; N, 9.67%; S, 11.45%.

INFRARED DATA (cm^{-1}). 685m, 735s, 745m, 830m, 850m, 1000w, 1060w, 1075s, 1140s, 1175m, 1270m, 1325s, 1360m, 1500s, 1550s, 1600m, 2800w, 3100s.

VISCOSITY: $[\eta] = 0.034$ dl/g at 25°C in DMSO as solvent.

MOLECULAR WEIGHT. $\bar{M}_w = 1190 \pm 7\%$.

4,4'-Diaminodiphenylsulfone-Dimethylolurea Copolymer (IIIh). Water (150 ml), 4.96 g (0.02 mole) 4,4'-diaminodiphenylsulfone, and 0.45 g (0.005 mole) oxalic acid were stirred and heated to reflux. To this solution was added 2.40 g (0.02 mole) dimethylolurea. Reflux was continued for 5 hr after which time the white polymer was collected by filtration. The product was washed several times in hot water and continuously extracted with methanol for 24 hr. The yield was 5.00 g. The copolymer had a softening temperature of 257–260°C.

ANAL. Calcd for $\text{C}_{87}\text{H}_{92}\text{N}_{22}\text{O}_{17}\text{S}_6$: C, 54.70%; H, 4.83%; N, 10.10%; S, 10.13%. Found: C, 59.02%; H, 4.94%; N, 12.79%; S, 11.79%.

INFRARED DATA (cm^{-1}). 685m, 710m, 815m, 1075s, 1125s, 1160m, 1250s, 1450s, 1550s, 1600s, 3100s.

VISCOSITY. $[\eta] = 0.049$ dl/g at 25° in DMSO as solvent.

MOLECULAR WEIGHT: $\bar{M}_w = 1925 \pm 7\%$.

Diazotization Reactions. The procedure employed was identical to that previously reported.⁵

Sulfanilic Acid-Dimethylolurea Copolymer (IIIb). Sulfanilic acid (3.46 g, 0.02 mole) was stirred and heated to reflux in 150 ml water. To the hot solution was added 2.40 g (0.02 mole) dimethylolurea. The clear solution changed to a bright strawberry-red color within 15 min, followed by a gradual transition to a bright-yellow color which persisted during the 5 hr reflux. The solution was allowed to cool, and enough dioxane was added to precipitate the resin. The product was washed several times with ethanol and dried at 110°C. The yield of light-yellow polymer was 3.80 g. The product was heat stable up to 300°C.

ANAL. Calcd for $C_{60}H_{72}N_{10}O_{27}S_7$: C, 42.00%; H, 4.20%; N, 15.52%; S, 13.00%. Found: C, 39.40%; H, 5.07%; N, 14.75%; S, 12.06%.

INFRARED DATA (cm^{-1}). 680w, 760w, 830w, 880w, 1033s, 1110m, 1175s, 1310w, 1360w, 1450m, 1550m, 1600s, 1660s, 2800m, 3200s.

VISCOSITY. $[\eta] = 0.088$ dl/g at 25° in DMSO as solvent.

MOLECULAR WEIGHT. $\bar{M}_w = 1710 \pm 7\%$.

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References

1. R. J. Cornell and L. G. Donaruma, *J. Polym. Sci.*, **3A**, 287 (1965).
2. R. J. Cornell and L. G. Donaruma, *J. Med. Chem.*, **8**, 388 (1965).
3. L. G. Donaruma and J. Razzano, *J. Med. Chem.*, **9**, 258 (1966).
4. J. R. Dombroski, L. G. Donaruma, and J. Razzano, *J. Med. Chem.*, **10**, 963 (1967).
5. J. R. Dombroski, L. G. Donaruma, and J. Razzano, *J. Med. Chem.*, **10**, 964 (1967).
6. N. A. Yaremchuk, L. M. Shuter, and Y. P. Berkman, *Dokl. Luovusk. Politekh. Inst.*, **5(1-2)**, 55 (1963); *C.A.*, **64**, 3874a (1966).

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