action was complete, 2-chloromethyl-5-methoxy-4H-pyran-4-one (II) (37.2 g, 0.212 mole), was added and the reaction mixture was stirred for 24 hr at room temperature. The DMF was distilled *in vacuo*, and the solid residue was extracted with hot $CHCl_3$–ethanol (80:20) and filtered. The filtrate was taken to dryness *in vacuo*, and the dark residue was recrystallized twice with charcoal treatment from ethanol–water. The resulting white needles weighed 33.7 g and had mp 179.5–181° (uncor).

*Anal.* Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.55; H, 4.91; N, 8.99.

**DL-4-Hydroxy-5-methoxy-2-pyridylalanine (IV).**—A mixture of 29.0 g of III and 60 g of concentrated $NH_4OH$ was placed in a stainless steel bomb; the bomb was sealed and placed in an oven at 85–90° for 2.5 hr. The reaction mixture, a dark liquid, was then concentrated *in vacuo*, and the residual $NH_4OH$ was removed by taking up the viscous residue in methanol and again concentrating *in vacuo*. The concentrate was ninhydrin positive (dark blue), but repeated attempts to effect crystallization were unsuccessful. Hydrolysis of this residue was effected by heating 28.0 g of the residue under reflux several hours in a suspension of 45 g of $Ba(OH)_2$ in 200 ml of water. After removal of solid $Ba(OH)_2$ by filtration, the filtrate was neutralized by the addition of $CO_2$ (Dry Ice). The $BaCO_3$ which precipitated was removed by filtration, and the filter cake was washed with water to remove any adsorbed amino acid. Remaining $Ba^{2+}$ was removed from the filtrate by addition of 10% $H_2SO_4$ until $BaSO_4$ no longer precipitated. After filtration the filtrate was concentrated *in vacuo*, and the light brown residue was recrystallized (after decolorization by charcoal treatment) from ethanol–water to yield 14.0 g of white, hygroscopic crystalline material, mp 252–255° dec. Paper chromatography of the product with BuOH–AcOH–$H_2O$ (4:1:1) gave a single ninhydrin spot (light brown), $R_f$ 0.13.

*Anal.* Calcd for $C_9H_{12}N_2O_4 \cdot 0.5H_2O$: C, 48.87; H, 5.92; N, 12.66. Found: C, 48.78; H, 6.10; N, 12.53.

**DL-4,5-Dihydroxy-2-pyridylalanine (V).**—A solution of 1.0 g of IV and 3 ml of concentrated HI was heated under reflux for 3.5 hr. The HI was then removed *in vacuo*, and the residue was taken up in a small volume of water. The resulting solution was neutralized with concentrated $NH_4OH$, whereupon a precipitate of the amino acid formed (the amino acid is sparingly soluble in water). Complete removal of the amino acid from solution was effected by the addition of ethanol, and the crystalline material was collected by filtration. After decolorizing with charcoal, the amino acid was finally recrystallized from ethanol–water, and after drying overnight at 80° (vacuum desiccator, $P_2O_5$) weighed 0.90 g, mp 236–241° dec. Paper chromatography of the amino acid in BuOH–AcOH–$H_2O$ (4:1:1) gave a single ninhydrin spot (light brown) with an $R_f$ of 0.13. The amino acid reacted with $FeCl_3$ to produce a deep purple color, indicating cleavage of the methoxy group in the 5 position of the pyridine ring.

*Anal.* Calcd for $C_8H_{10}N_2O_4 \cdot H_2O$: C, 44.45; H, 5.60; N, 12.96. Found: C, 44.23; H, 5.58; N, 12.82.

Ultraviolet absorption spectrum showed at pH 3, $\lambda_{max}$ 270 mμ, $\lambda_{min}$ 256 mμ; at pH 12, $\lambda_{max}$ 294–296 mμ, $\lambda_{min}$ 250–252 mμ. These absorption maxima and minima were identical with those of a sample of 4,5-dihydroxy-2-hydroxymethylpyridine.

## Synthetic Biologically Active Polymers. IV. $N^1$-Acylsulfanilamide–Formaldehyde Copolymers

JOHN R. DOMBROSKI, L. GUY DONARUMA, AND JOHN RAZZANO[2]

*Department of Chemistry, Clarkson College of Technology, Potsdam, New York*

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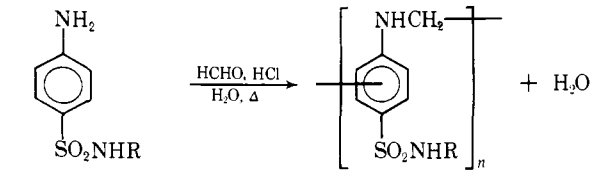
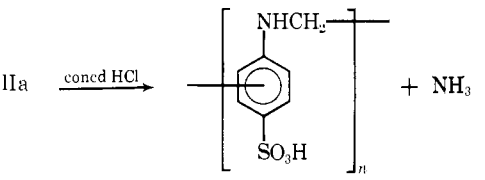
In continuing investigations aimed at attempting to discern the effect of polymerization on drugs, we had occasion to study the copolymerization of sulfanilamide (Ia), sulfabenzamide (Ib), and sulfacetamide (Ic) with formaldehyde.

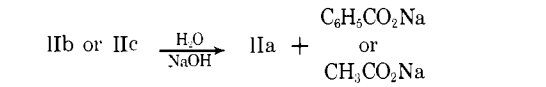


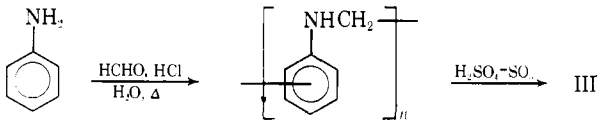

Ia, R = H
Ib, R = $C_6H_5CO$
Ic, R = $CH_3CO$

IIa, R = H
IIb, R = $C_6H_5CO$
IIc, R = $CH_3CO$




III




IV

The copolymerization processes were carried out, in general, by the method previously reported.[1a] Hydrolysis of IIa with concentrated HCl yielded III. The structure of III was previously related[1a] to the structure of a polymer obtained by the sulfonation of an aniline–formaldehyde copolymer (IV). Basic hydrolysis of both IIb and IIc yielded IIa. Acidic hydrolysis of IIa derived from both IIb and IIc yielded III. Elemental analyses and infrared spectra seem to confirm the assigned structures.

The copolymers appeared to be monodisperse. The intrinsic viscosities of IIa, IIb, and IIc in dimethyl sulfoxide (DMSO) at 25° were found to be 0.07, 0.24, and 0.10, respectively.

It was reported previously that a sulfapyridine–formaldehyde copolymer exhibited antimalarial activity above that of sulfapyridine *per se*.[1a] Therefore, copolymers IIa–c were screened for antimalarial activity employing the procedure previously reported.[1a] The screening results are summarized in Table I.

### Experimental Section

**Sulfanilamide–Formaldehyde Copolymer (IIa).**—A mixture containing 1.67 g (0.0097 mole) of sulfanilamide (Ia), 50 ml of water, 1 ml of 4% aqueous HCl, and 1 ml of 37% aqueous formaldehyde solution was heated at reflux for 8 hr. A resin was deposited. The reaction mixture was cooled and filtered. The resin was pulverized and extracted with boiling water several times to remove unreacted monomers. The yield of dry washed product was 1.03 g (57.8%). The product softened at 187–190°. The intrinsic viscosity of the product in DMSO was 0.07; infrared data ($cm^{-1}$): 3400 w, 3250 s, 3100 s, 2910 m, 2800 w, 2300 w, 1650 m, 1570 s, 1490 s, 1390 w, 1290 s, 1140 s, 1080 s, 990 m, 885 w, 820 s.

*Anal.* Calcd for $C_7H_8N_2O_2S$: C, 45.6; H, 4.37; N, 15.20; S, 17.40. Found: C, 43.95; H, 5.03; N, 14.30; S, 16.00.

(1) For previous papers in this series see: (a) L. G. Donaruma and J. Razzano, *J. Med. Chem.*, **9**, 258 (1966); (b) R. J. Cornell and L. G. Donaruma, *J. Polymer Sci.*, **3A**, 827 (1965); *J. Med. Chem.*, **8**, 388 (1965).

(2) This work was taken in part from the thesis to be submitted by Mr. John Razzano in partial fulfillment of the requirements for the Ph.D. degree.

TABLE I
ANTIMALARIAL SCREENING DATA[a] FOR COPOLYMERS IIa–c

| System | Dose level, mg/kg | Monomer act. (I)[b] | Polymer act. (II)[b] |
|---|---|---|---|
| Ia, IIa | 80 | Inactive | Inactive |
| | 160 | Inactive | Inactive |
| | 320 | Active | Inactive |
| | 640 | Active | Curative |
| | 1280 | Active | Curative |
| Ib, IIb | 40 | Curative | Inactive |
| | 160 | Curative | Toxic |
| | 640 | Curative | Toxic |
| Ic, IIc | 40 | Inactive | Curative |
| | 160 | Curative | Curative |
| | 640 | Curative | Curative |

Antimalarial testing was done by Dr. Leo Rane at the University of Miami Medical School. Tests were carried out employing *Plasmodium berghei* in young ICR/Ha Swiss mice. [b] Active = mice in a treated group survive at least 14 days; curative = mice in a treated group survive to 30 days; toxic = deaths occurring through day 5 after infection are attributed to drug action; Control animals do not die before day 6.

**Sulfabenzamide–Formaldehyde Copolymer (IIb).**—A mixture of 1.37 g (0.005 mole) of sulfabenzamide (Ib), 50 ml of water, 1.1 ml of 37% aqueous HCl, and 1 ml of 37% aqueous formaldehyde solution was refluxed for 5.5 hr. A pale yellow resin was precipitated which adhered to the container walls. The reaction mixture was cooled and the liquid was decanted off. The resin was dissolved in the minimum amount of hot dimethylformamide (DMF) and the product precipitated from the DMF solution by addition of water. The product was filtered, reprecipitated again from DMF with water, filtered, and air dried. The yield of pale yellow solid softening at 193–197° was 0.95 g (66%). The intrinsic viscosity of the product in DMSO at 25° was 0.24; infrared data ($cm^{-1}$): 3600 w, 3550 m, 3375 s, 3220 m, 3050 w, 2875 w, 2315 w, 1775 s, 1590 s, 1500 m, 1460 s, 1425 s, 1380 w, 1340 s, 1250 m, 1175 s, 1160 s, 1085 s, 1065 m, 1030 w, 1000 w, 950 w, 885 m, 830 m.

*Anal.* Calcd for $C_{13}H_{12}N_2O_3S$: C, 58.31; H, 4.79; N, 9.72. Found: C, 58.39; H, 5.11; N, 9.02.

**Sulfacetamide–Formaldehyde Copolymer (IIc).**—The procedure for the preparation of IIb was repeated employing 1.99 g (0.01 mole) of sulfacetamide (Ic) in place of Ib and 1 ml of 3.7% aqueous HCl instead of 1.1 ml of 37% aqueous HCl. The yield of product softening at 230–235° was 0.3 g (14.2%). The intrinsic viscosity of the copolymer in DMSO at 25° was 0.10; infrared data ($cm^{-1}$): 3585 m, 3535 m, 3350 s, 3230 s, 3050 m, 2860 w, 2610 w, 2320 w, 1700 w, 1695 m, 1595 s, 1500 m, 1445 m, 1375 w, 1325 s, 1240 w, 1220 w, 1165 s, 1155 s, 1095 m, 1000 w, 950 w, 900 w, 835 w.

*Anal.* Calcd for $C_9H_{10}N_2O_3S$: C, 47.77; H, 4.45; N, 12.39; S, 14.15. Found: C, 46.45; H, 4.26; N, 13.01; S, 14.95.

**Hydrolysis of IIa.**—Hydrolysis of IIa was carried out as reported previously for a sulfapyridine–formaldehyde copolymer.[1a] When the reaction mixture was made basic, the odor of ammonia was apparent. The solution was evaporated to dryness after reacidification. The residue was thoroughly washed with water to remove the salt present. The brown solid left was identical with the sulfonic acid hydrolysis product derived from hydrolysis of the sulfapyridine–formaldehyde copolymer.[1a]

**Hydrolysis of IIb.**—IIb (6.5 g) was dissolved in 50 ml of 10% aqueous NaOH and refluxed for 8 hr. The solution was cooled and the pH was adjusted to 8 with dilute aqueous HCl. The gummy precipitate (3.5 g) was washed with HCl after filtration and dried. The infrared spectrum of this material was comparable to that of IIa, and acid hydrolysis of this product[1a] yielded III. The filtrate at pH 8 was made strongly acidic with HCl, and 2.2 g (96%) of benzoic acid (identified by infrared comparison) was precipitated.

**Hydrolysis of IIc.**—IIc (2.0 g) was dissolved in 12 ml of 10% aqueous NaOH and refluxed 24 hr. The solution was cooled and carefully neutralized to pH 8. A precipitate appeared which was collected by filtration, washed with water, and dried to yield 1.45 g of material having an infrared spectrum comparable to IIa, and acid hydrolysis of this product yielded III. The filtrate at pH 8 was made strongly acid with aqueous HCl. The odor of acetic acid was apparent, but no attempt was made to achieve quantitative isolation.

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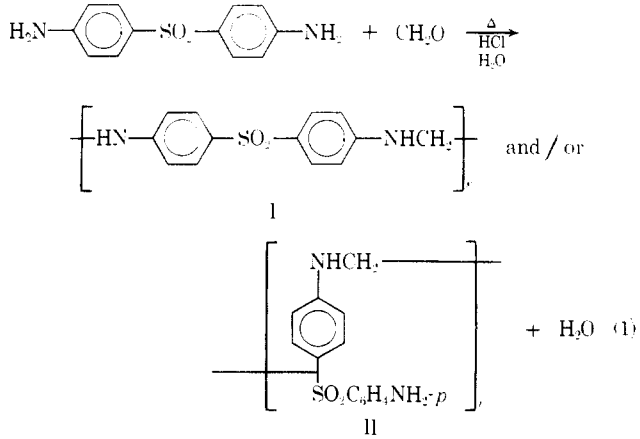
## Synthetic Biologically Active Polymers. V. 4,4′-Diaminodiphenyl Sulfone–Formaldehyde Copolymer[1]

JOHN R. DOMBROSKI, L. GUY DONARUMA, AND JOHN RAZZANO

*Department of Chemistry, Clarkson College of Technology, Potsdam, New York 13676*

*Received May 22, 1967*

Previous articles in this series[2] have dealt with the preparation, characterization, and properties of new polymeric tropolone derivatives[2a] and a novel sulfapyridine–formaldehyde copolymer.[2b] This report concerns itself with the copolymerization of 4,4′-diaminodiphenyl sulfone (DDS) and formaldehyde. Reaction of DDS and formaldehyde in refluxing aqueous HCl (see eq 1) yielded a solid material which softened at 235° and whose infrared spectrum and analysis indicated that it possessed either structure I or structure II. Structures I and II also would be expected by analogy with similar reactions.[2b] The product was soluble in aqueous HCl, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF).




$$[\eta] = K\bar{M}^{a} \quad (2)$$

$[\eta]$ = intrinsic viscosity
$\bar{M}$ = average molecular weight
$K$ and $a$ = empirical constants

In order to differentiate between the two possibilities, or to recognize the presence of both structures in the product, the purified reaction product was treated with aqueous nitrous acid to diazotize any free amino groups present. Upon warming the solution and col-

(1) This work was taken in part from the thesis to be submitted by Mr. John Razzano in partial fulfillment of the requirements for the Ph.D. degree.

(2) (a) R. J. Cornell and L. G. Donaruma, *J. Med. Chem.*, **8**, 388 (1965); R. J. Cornell and L. G. Donaruma, *J. Polymer Sci.*, **3A**, 827 (1965); (b) L. G. Donaruma and John Razzano, *J. Med. Chem.*, **9**, 258 (1966).