Synthetic Biologically Active Polymers. III. A Sulfapyridine–Formaldehyde Copolymer

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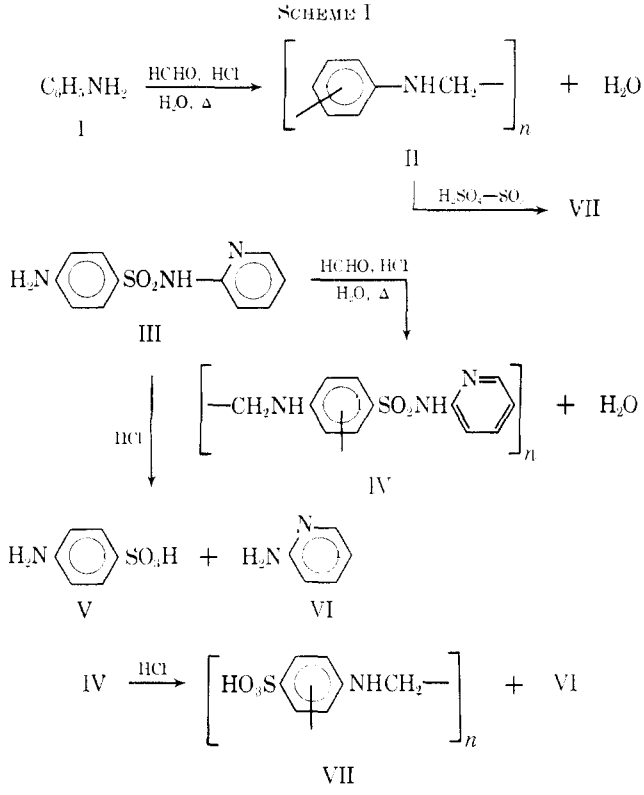
In investigations concerning the effect of polymerization on the biological activity of drugs,[1] we have prepared formaldehyde copolymers of a number of sulfonamide drugs. This report concerns the preparation, characterization, and properties of a sulfapyridine–formaldehyde copolymer.

The condensation of aniline (I) with formaldehyde to yield polymers related to II is a known reaction[2] (see Scheme I). Structurally, sulfapyridine (III) is

SCHEME I



similar to aniline with regard to polymerization enhancing functionality. In addition, sulfanilamide is reported to copolymerize with formaldehyde, and sulfonamide drugs are known to condense with formaldehyde.[3] By analogy, condensation of III with formaldehyde should yield IV. Upon carrying out this reaction in refluxing aqueous hydrochloric acid, a polymer was obtained. No appreciable cleavage of the sulfonamide linkage was observed. Elemental analyses and infrared spectra appeared to confirm structure IV. In order to obtain chemical evidence for the assigned structure, IV was hydrolyzed with aqueous acid according to the procedure of Northey for the cleavage of sulfapyridine[4] to sulfanilic acid (V) and 2-aminopyridine (VI). Hydrolysis of IV gave an 80% recovery of 2-aminopyridine along with the expected sulfanilic acid–formaldehyde copolymer (VII). VII could not be synthesized from sulfanilic acid (V) and formaldehyde, but it was possible to synthesize such a polymer by sulfonation of II. The infrared spectrum of VII was comparable with that of the polymer prepared by sulfonation of II.

The slightly off-white solid IV softened at 80° and was soluble in dimethylformamide (DMF) and dilute hydrochloric acid. The polymer was polydisperse and of low molecular weight. Fractionation by precipitation techniques employing DMF and water yielded 12 fractions. The inherent viscosity of the polymer was 0.080 and those of the fractions derived from it ranged from 0.027 to 0.10.

It is known that some sulfonamide drugs show antimalarial activity.[4] Unfractionated IV was screened employing *Plasmodium berghei* in young ICR/Ha Swiss mice.[5] Concurrently, control tests were run employing identical dosages of sulfapyridine. Tests carried out at five different dose levels (1280, 640, 320, 160, and 80 mg/kg) for both IV and sulfapyridine showed that IV was curative at all dose levels whereas sulfapyridine was curative only at doses of 1280 and 640 mg/kg. Preliminary screening tests on the polymer fractions indicate that the activity may be concentrated in the fractions of medium inherent viscosity (η = 0.04–0.06).

Experimental Section

Sulfapyridine–Formaldehyde Copolymer (IV).—Water (100 ml), 1.0 ml of 8% aqueous HCl, and 1.23 g (0.005 mole) of sulfapyridine were heated to reflux. To this solution was added 1.0 ml (0.012 mole) of 37% aqueous formaldehyde solution. The solution turned milky and within 30 min, a resinous material formed on the walls of the container. The mixture was refluxed for an additional 6 hr, and the supernatant liquid was decanted. The resinous material remaining in the container was allowed to cool, washed from the container with water, and filtered. The yield of crude dry powder was 0.7 g (68%). The powder was dispersed in 100 ml of boiling water. The liquid was decanted away from the fused resin and the extraction procedure was repeated again. The yield of product freed from excess sulfapyridine was 0.52 g (50%). The product softened at 80° and decomposed at 152–162°. The inherent viscosity of the product at 25° in dimethylformamide was 0.080; infrared data (cm^{-1}): 675 w, 775 m, 825 w, 945 w, 1000 w, 1080 m, 1130 s, 1260 m, 1380 m, 1500 m, 1590 s, 1630 m, 2910 w, 3230 w, 3400 m.

Anal. Calcd for $C_{9}H_{10}N_{2}O_{2}S$: C, 55.20; H, 4.21; N, 16.1; S, 12.3. Found: C, 54.45; H, 4.57; N, 16.2; S, 12.45.

Hydrolysis of IV.—Three grams of IV was dissolved in 12 ml of concentrated HCl and the solution refluxed for 20 hr. The solution was concentrated to 10 ml and made basic with 25% aqueous NaOH. The solution was extracted with five 25-ml portions of ether. The combined extracts were dried ($MgSO_4$), and the solvent was removed to leave a residue of 0.95 g (80%) of 2-aminopyridine (VI) which was identical in all respects with an authentic sample. The basic aqueous phase was acidified and evaporated to dryness. The residue was thoroughly washed with water to remove the salt. A brown powder (VII) (1 g) which did not soften or melt below 300° remained. This product

(1) R. J. Cornell and L. G. Donaruma, *J. Polymer Sci.*, **3A**, 827 (1965); L. G. Donaruma and R. J. Cornell, *J. Med. Chem.*, **8**, 388 (1965).

(2) K. H. Meyer, "Natural and Synthetic High Polymers," Interscience Publishing Co., Inc., New York, N. Y., 1950, pp 279–281; R. R. Bishop, *J. Appl. Chem.*, **6**, 256 (1956); Y. Agata, M. Okano, and M. Sugawara, *J. Am. Chem. Soc.*, **73**, 1715 (1951); K. Frey, *Helv. Chim. Acta*, **18**, 491 (1935).

(3) J. M. Camps, Spanish Patent 218,211 (1954); E. Fujiwara, *J. Pharm. Soc. Japan*, **66**, 41 (1946); J. Druey and A. Becker, *Helv. Chim. Acta*, **31**, 2184 (1948).

(4) E. H. Northey, "The Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1960, pp 14, 800–808; M. L. Crossley, E. H. Northey, and M. E. Hultquist, *J. Am. Chem. Soc.*, **62**, 372 (1940).

(5) Antimalarial screening was carried out by Dr. L. Rane of the University of Miami Medical School.

showed a strong infrared absorption band, typical of sulfonic acids, at 1033 cm^{-1}; infrared data (cm^{-1}): 695 m, 770 w, 825 w, 1033 s, 1160 s, 1500 m, 1600 m, 1625 s, 1650 m, 2900 w, 3400 s.

Aniline–Formaldehyde Copolymer (II).—A solution containing 8 ml (0.088 mole) of aniline, 400 ml of water, and 3 ml of concentrated HCl was heated to incipient reflux, and 8 ml (0.099 mole) of 37% of CH_2O solution was added. The solution became turbid, and within 60 sec, oily droplets appeared. The mixture was refluxed for 4 hr, and the hot supernatant liquid was decanted. The resin was allowed to solidify, powdered, and washed with warm water. The yield of product melting at 85–120° was 5.5 g; infrared data (cm^{-1}): 690 w, 750 m, 815 m, 940 w, 1260 w, 1310 w, 1520 s, 1620 s, 2850 m, 3000 m, 3330 m.

Sulfonation of the Aniline–Formaldehyde Copolymer (VII).—Two grams of powdered II was added with strong agitation to 12 ml of fuming H_2SO_4. The solution was heated at 70° for 2.5 hr and then added slowly, with caution, to 250 g of crushed ice. The acid solution was made basic with $CaCO_3$ and the precipitated $CaSO_4$ removed by filtration. The filtrate was then carefully treated with sufficient Na_2CO_3 to convert the calcium sulfonate salt of VII to the sodium salt. The precipitated $CaCO_3$ was filtered off, and the filtrate was evaporated almost to dryness. The residue was treated with 10 ml of concentrated HCl, and the brown precipitate was collected by filtration and dried under vacuum. The product did not soften or melt below 300°. A strong infrared absorption band characteristic of the sulfonic acid group appeared at 1032 cm^{-1}. The infrared spectrum of this material was comparable to that of VII prepared by the hydrolysis of IV; infrared data (cm^{-1}): 750 w, 830 w, 900 w, 1032 s, 1200 s, 1300 m, 1490 m, 1595 m, 1660 m, 3000 m, 3400 s.

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Synthesis of Substituted β-Lactams

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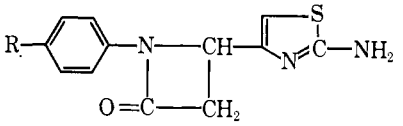
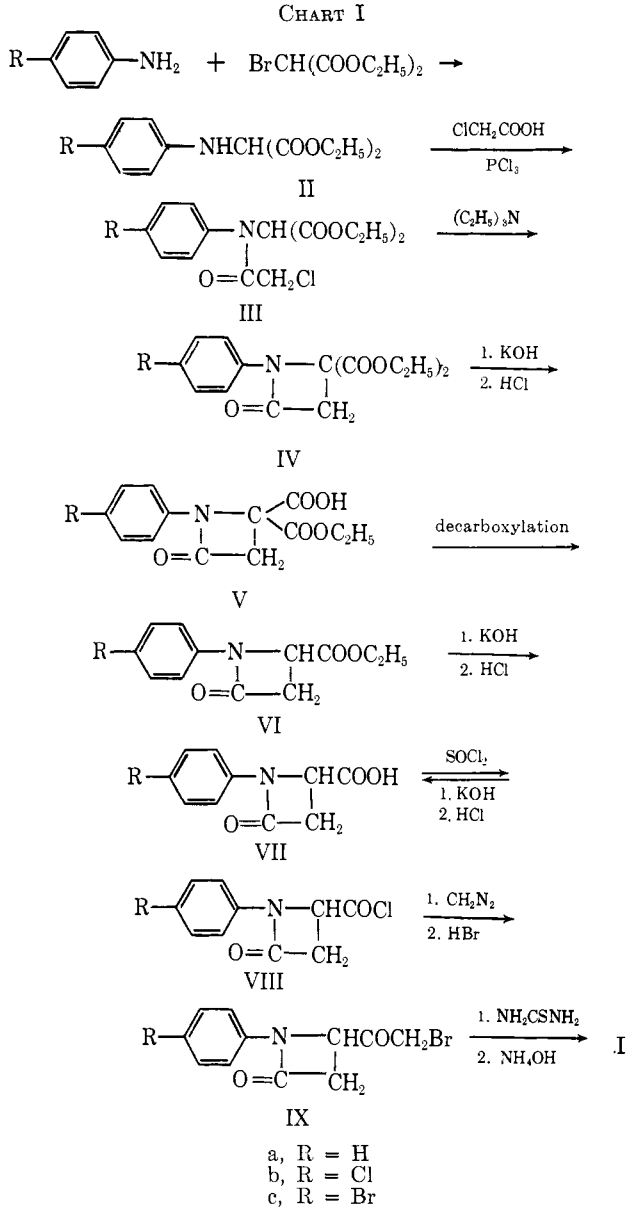
In view of the β-lactam structure in such biologically important compounds as the penicillins and cephalosporins, it was thought of interest to place this ring between *para*-substituted phenyl and thiazolyl functions. The latter two occur in 4-aminophenyl (2-amino-5-thiazolyl) sulfone (Promizole)[1] and its cyclopropane analog.[2] The synthesis of three β-lactams (I) is recorded in this note.



I

Several methods[3–6] are available for the synthesis of β-lactams, but some of them are not very general in applicability; furthermore, the yields are very different with the same method for different substituted β-lactams. We have chosen the method developed by Sheehan and Bose[7,8] for the synthesis of the β-lactam moiety of compounds of type I. The sequence of reactions used is shown in Chart I.

CHART I



a, R = H
b, R = Cl
c, R = Br

These β-lactam derivatives proved to be of little biological interest. They were found to be inactive when tested *in vitro* against several species of protozoa and against *Escherichia coli* (at 1 mg/ml). Little CNS activity was exhibited in mice. In preliminary enzyme screens Ia was found to be inactive. Diuretic activity of Ib was determined in rats dosed at 5 and 50 mg/kg intraperitoneally[9]; the compound was found to be inactive although it exhibited some toxicity. Table I summarizes the properties of the compounds prepared during this investigation.

Experimental Section[10]

A typical procedure for the synthesis of compounds of type I is described below in the preparation of 1-*p*-chlorophenyl-4-(2-aminothiazolyl)-2-azetidinone (Ib).

(1) L. L. Bambas, *J. Am. Chem. Soc.*, **67**, 671 (1945).
(2) D. G. Markees and A. Burger, *ibid.*, **70**, 3329 (1948).
(3) H. Staudinger, "Die Ketene," F. Enke, Stuttgart, 1912.
(4) H. Staudinger, H. W. Klever, and P. Kober, *Ann.*, **374**, 1 (1910).
(5) R. Breckpot, *Bull. Soc. Chim. Belges*, **32**, 412 (1923).
(6) H. Gilman and M. Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).
(7) J. C. Sheehan and A. K. Bose, *ibid.*, **72**, 5158 (1950).
(8) J. C. Sheehan and A. K. Bose, *ibid.*, **73**, 1261 (1951).
(9) J. E. Baer and K. H. Beyer, *Am. J. Pharm.*, **132**, 5 (1960).
(10) Infrared spectra were kindly determined by Professor A. K. Bose of Stevens Institute of Technology, and Dr. I. P. Varshney of Aligarh University, India. Melting points and boiling points are uncorrected.