0.004 to 0.0008 g. per ml. of *m*-cresol or dimethylformamide.

In some cases it was necessary to fractionate the polymers in order to obtain straight line viscosity relationships. Polyurethans IV and V were fractionally precipitated using an acetone–methanol system. Polyurethan VIII was similarly handled with an acetone–*n*-hexane mixture. Nitrogen analysis of the first and fifth fractions of IV indicated that the fractions were the same in chemical composition. Viscosity determinations of the first and fifth fractions of IV and VIII indicated that the fractionations had been effective in narrowing the molecular weight distribution of the material.

Infrared Analysis.—The infrared absorption spectra were taken on a Baird Associates, Inc., Model B infrared recording spectrophotometer. When it was not possible to form films of the material, as was the case with polyhexamethyleneurea, Nujol mulls of finely divided polymer were used.

Homopolymer[24] of Methylene-bis-(4-phenyl Isocyanate).—When solutions of this diisocyanate in anhydrous and peroxide-free ether, dioxane, tetrahydrofuran or chlorobenzene were treated with a few drops of triethylamide, a white precipitate appeared in a few minutes at room temperature. The copper chelate of acetylacetone also catalyzed the formation of this substance. In tetrahydrofuran with no catalyst the product started to appear after about 30 hours. The substance was not soluble in common solvents except dimethylformamide. For analysis a sample was prepared in ether and washed thoroughly with benzene to remove monomer. The polymer softened and slowly discolored above 205–210°, with no sharp decomposition point.

Anal. Calcd. for $(C_{15}H_{10}O_2N_2)_x$: N, 11.20. Found: N (Dumas), 11.16. No attempt was made to determine molecular weight.

Hydrolysis of the Phenolic Polyurethans VI and VII.—To 0.0027 mole of the respective polyurethan contained in a 500-ml., three-neck, round-bottom flask equipped with a thermometer and reflux condenser and protected from atmospheric carbon dioxide with an ascarite tube were added exactly 200 ml. of 0.2192 *N* sodium hydroxide solution and a small amount of Duponol ME as wetting agent. After standing six days at 90° the mixture was cooled and the solution separated from the solid material by vacuum filtration through a weighed sintered glass funnel. The solid material was washed thoroughly with water and dried to constant weight. The substance softened at 245–250° and became fluid at 260–270°. It was partly soluble in *m*-cresol. The same substance was obtained by hydrolysis of both VI and VII.

Anal. Calcd. for $(C_7H_{14}N_2O)_x$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.90; H, 9.86; N, 18.17.

Although the analytical results indicate that this substance was not homogeneous, the infrared absorption spectra were practically identical with that of an authentic specimen[12] of polyhexamethyleneurea. Hydrolysis product of VI or VII: $\lambda_{max}^{mineral\ oil}$ 2.34(w), 3.01(s), 6.17(s), 6.38(m), 7.99(m), 8.25(w), 9.25(w), 13.83(m). Known polyhexamethyleneurea: $\lambda_{max}^{mineral\ oil}$ 2.33(w), 3.05(s), 6.19(s), 6.43(m), 8.02(m), 8.30(w), 9.25(w), 13.83(m). Polyurethan VI: $\lambda_{max}^{mineral\ oil}$ 2.35(w), 3.01(w), 4.32(m), 5.89(s), 8.27(s), 8.52(m), 9.84(w), 13.84(s).

Aliquot portions (20 ml.) of the hydrolysis filtrate after removal of the polyurea were titrated with standard 0.1 *N* hydrochloric acid using a Beckman model M *p*H meter with glass electrode.

The equivalence points were found from the differential plot of $\Delta p\mathrm{H}/\Delta v$ against v of acid. Control experiments with known mixtures of the diamine, sodium carbonate and sodium hydroxide showed that the amount of carbonate and diamine could be determined by a single titration with an accuracy of 1%. The amount of carbonate was also found by liberation of carbon dioxide and absorption in a weighed ascarite tube.

The amount of free dihydroxy compound present was found by continuous extraction of an acidified aliquot sample and evaporation of the ether extract. In the case of resorcinol this method gave an unreasonably high value, while an attempted iodimetric titration gave low values.

Aminolysis of VI.—To a 0.500-g. sample of VI in a 500-ml., three-neck, round-bottom flask equipped with a thermometer and reflux condenser was added 100 ml. of an aqueous solution of 1,6-hexamethylenediamine (0.293 g. diamine/100 ml. of water). After heating at 90° for six days the solid material (0.460 g.) was separated from the solution by filtration through a weighed sintered glass funnel. Bisphenol A (0.0381 g.) was isolated from a 20-ml. aliquot of the filtrate by continuous ether extraction.

The polymeric substance softened at 245–250°, and was soluble only in *m*-cresol, whereas the original polyurethan melted at 130° and was soluble in acetone. The infrared absorption spectrum showed the prominent urea bands at 6.2 and 6.4 μ, characteristic of polyhexamethyleneurea and had only a trace of the bands given by the original polyurethan.

NEWARK, DELAWARE

(24) A review of work on isocyanate homopolymers is given by J. H. Saunders and R. J. Slocombe, *Chem. Revs.*, **43**, 203 (1948).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Acetylation of Some Sulfapyrimidines

BY J. B. ZIEGLER AND A. C. SHABICA

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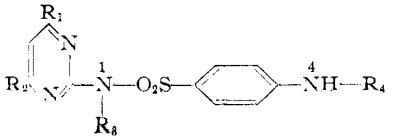
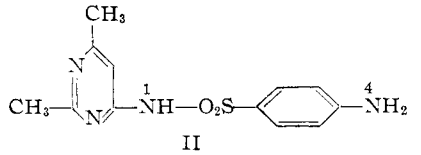
It has been shown that acetylation with excess acetic anhydride in pyridine affords monoacetyl derivatives of sulfadiazine, sulfamerazine and Elkosan, but gives a diacetyl derivative of sulfamethazine. However, acetylation of sulfamethazine with excess acetic anhydride in glacial acetic acid yields a monoacetyl derivative. A mechanism is suggested to account for these facts.

During the course of a study of the solubility of a number of substituted sulfonamides, to be reported elsewhere, it was necessary to synthesize the N^4-monoacetyl derivatives of sulfadiazine (Ia), sulfamerazine (Ib), sulfamethazine (Ic) and Elkosin



Ia, $R_1 = R_2 = R_3 = R_4 = H$;
Ib, $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$;
Ic, $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$



II

Id, $R_1 = R_2 = CH_3$, $R_3 = H$, $R_4 = CO\text{–}CH_3$
Ie, $R_1 = R_2 = CH_3$, $R_3 = R_4 = CO\text{–}CH_3$

(II). A general procedure was devised which involved heating the free sulfonamide with an excess of acetic anhydride in pyridine solution. This method yielded the desired N^4-monoacetyl derivatives with all sulfapyrimidines with the

single exception of sulfamethazine. It was noted that in this case the acetylated product precipitated rapidly from the hot reaction mixture whereas in all other cases cooling and dilution with water was required to induce crystallization. After isolation, this acetylated sulfamethazine proved to be very much less soluble in aqueous media than had been anticipated, especially at *p*H values above 7. Microanalysis showed that it had the composition of a diacetyl, and not a monoacetyl, sulfamethazine.

The authentic N^4-monoacetylsulfamethazine (Id) was finally prepared according to the method of Rose and Swain,[1] in which glacial acetic acid in place of pyridine is used as solvent. Curiously enough, the two acetyl derivatives proved to have the same melting point (248–250°) except that the diacetyl derivative melted *with decomposition*. Admixture of the two depressed the melting point to 238–244° dec. It was found that the diacetyl derivative could be converted to the N^4-monoacetyl derivative by a mild hydrolysis in hot aqueous sodium bicarbonate solution. This fact, together with the very sparing solubility in alkaline solution leads to the formulation of this apparently new substance as the N^1,N^4-diacetylsulfamethazine (Ie). The possibility remains that the second acetyl group might have entered the pyrimidine ring. However, this formulation implies a considerable degree of bond stabilization in the pyrimidine ring and, in consequence, the presence of imino (—C=N—) groups. The infrared absorption spectrum of the diacetylsulfamethazine lacks the band in the 1640–1670 $cm.^{-1}$ region which is characteristic of this group.

It seems possible that electron release to the N^1-nitrogen occasioned by the two methyl groups in the pyrimidine ring may play a role in the formation of the diacetyl derivative of sulfamethazine in pyridine solution, assuming an electrophilic attack by acetylium ion. In acetic acid, this effect would appear to be counterbalanced by the placement of a positive charge on the ring nitrogen. Banks[2] and Tomisek and Christensen[3] have developed this effect in detail. The failure of Elkosin to produce a diacetyl derivative in pyridine may be attributable to the different nature of the 2- and 4-positions in pyrimidines. Gabriel and Stelzner,[4] among others, have pointed out a difference in reactivity of this type.

(1) F. L. Rose and G. Swain, *J. Chem. Soc.*, 689 (1945).
(2) C. K. Banks, THIS JOURNAL, **66**, 1127 (1944).
(3) A. J. Tomisek and B. E. Christensen, *ibid.*, **67**, 2112 (1945).
(4) S. Gabriel and R. Stelzner, *Ber.* **29**, 1300 (1896).

Experimental[5]

General Procedure for Acetylation of Sulfapyrimidines.—A mixture of 2.00 g. (0.0072–0.008 mole) of the sulfapyrimidine, 4 ml. (4.3 g., 0.042 mole) of acetic anhydride and 10 ml. of pyridine was heated on the steam-bath for 45 minutes. The reaction mixture was cooled, diluted with about 40 ml. of water and chilled in the refrigerator. The solid was collected on a buchner funnel, washed with water and dried on the steam-bath. When necessary, the crude product so obtained was purified by recrystallization from boiling water. Samples were dried for microanalysis for two hours at 100° and 1 mm. pressure.

(a) N^4-Monoacetylsulfadiazine[6]: white crystals, m.p. 262–263° dec. *Anal.* Calcd. for $C_{12}H_{12}N_4O_3S \cdot {}^1/_4H_2O$: C, 48.56; H, 4.25; N, 18.88. Found: C, 48.63; H, 4.56; N, 18.74.

(b) N^4-Monoacetylsulfamerazine[6]: white crystals, m.p. 249.5–253°. *Anal.* Calcd. for $C_{13}H_{14}N_4O_3S$: C, 50.97; H, 4.61; N, 18.29. Found: C, 50.95; H, 4.89; N, 18.27.

(c) N^4-Monoacetyl Elkosin[7]: white crystals, m.p. 310–315° dec. *Anal.* Calcd. for $C_{14}H_{16}N_4O_3S$: C, 52.48; H, 5.03; N, 17.49. Found: C, 52.13; H, 5.33; N, 17.23.

(d) N^1,N^4-Diacetylsulfamethazine: white crystals, m.p. 248–250° dec. *Anal.* Calcd. for $C_{16}H_{18}N_4O_4S$: C, 53.03; H, 5.01; N, 15.46. Found: C, 53.36; H, 5.14; N, 15.58.

N^4-Monoacetylsulfamethazine.—This substance was prepared by the method of Rose and Swain[1]; white crystals, m.p. 248–250° *without decomposition*. Mixed with the diacetyl derivative described above (m.p. 248–250° dec.), m.p. 238–244° dec.

Anal. Calcd. for $C_{14}H_{16}N_4O_3S$: C, 52.48; H, 5.03; N, 17.49. Found: C, 52.61; H, 5.28; N, 17.56.

Mild Hydrolysis of N^1,N^4-Diacetylsulfamethazine.—A mixture of 1.00 g. of diacetylsulfamethazine (0.00276 mole), 0.26 g. of sodium bicarbonate (0.00304 mole) and 40 ml. of water was refluxed for 17 hours. The hot solution was decanted from a trace of undissolved material, acidified with acetic acid and cooled to room temperature. The solid was collected on a buchner funnel, washed with water and dried on the steam-bath. The product weighed 0.40 g., m.p. 248–252°. The melting point of a mixture of this material with an authentic specimen of N^4-monoacetylsulfamethazine (m.p. 249–253°) showed no depression. A mixture with diacetylsulfamethazine (m.p. 250–252° dec.), had m.p. 240–248° dec.

Acknowledgments.—We are indebted to Mr. R. E. Bagdon for technical assistance, and to Mr. Louis Dorfman and his associates for the microanalyses and for the determination and interpretation of the infrared absorption curves.

SUMMIT, NEW JERSEY

(5) All melting points were determined by the capillary tube method in an electrically-heated metal block and are compensated for the stem correction of the thermometer.
(6) R. O. Roblin, Jr., *et al.*, THIS JOURNAL, **62**, 2002 (1940). Correct C, H and N analyses for anhydrous acetylsulfadiazine are given.
(7) British Patent 565,501; *C. A.*, **40**, 5208 (1946).