[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES]

Penicillin Sulfoxides and Sulfones

ALFRED W. CHOW, NORMAN M. HALL, AND JOHN R. E. HOOVER

Received October 18, 1961

The preparation of sulfoxides and sulfones of benzylpenicillin and phenoxymethylpenicillin is described. The free acid derivatives were obtained by oxidizing the corresponding benzyl ester of the penicillin followed by removal of the benzyl grouping by hydrogenolysis.

Benzylpenicillin sulfone methyl ester[1] and benzylpenicillin sulfoxide methyl ester[2] were among the early derivatives of penicillin which were prepared. When tested in mice the sulfone methyl ester was found to have about one tenth the activity of benzylpenicillin, while the sulfoxide methyl ester was found to be inactive.[3] However, these sulfone and sulfoxide esters were reported to exhibit pronounced acid stability.[2,4] Penicillin esters, in general, are inactive *in vitro* as well as *in vivo*, and the protective action exhibited by certain penicillin esters in mice[5] was primarily due to the *in vivo* hydrolysis of the esters to free penicillins, an ability which is peculiar to mice and is completely lacking in higher animals.[6]

From these considerations, it appeared likely that the lack of activity shown by the benzylpenicillin sulfoxide and sulfone methyl esters was due to the fact that the required free carboxyl group was esterified. Since the free acid forms of the penicillin sulfoxides and sulfones have not been previously described, several of these derivatives were made with the hope that they might have a higher degree of activity than the corresponding esters and, possibly, also exhibit desirable properties not shown by the conventional penicillins.

Previously, the preparation of benzylpenicillin sulfoxide had been attempted unsuccessfully by the oxidation of both the sodium and the trimethylamine salts of benzylpenicillin with potassium permanganate in neutral phosphate buffer.[7] The corresponding methyl ester had been prepared by oxidizing benzylpenicillin methyl ester with sodium metaperiodate,[3] and benzylpenicillin sulfone methyl ester had been prepared by the oxidation of benzylpenicillin methyl ester with potassium permanganate.[1] The methods used for making the ester derivatives are not applicable to the preparation of the free acid forms of the penicillin sulfones or sulfoxides, and consequently these compounds have not been reported in the literature.

We have accomplished the preparation of penicillin sulfones and sulfoxides as the free acids *via* their benzyl esters. The benzyl grouping on the carbonyl moiety permitted the oxidation of the sulfur atom to proceed successfully, and it was readily removed subsequently by catalytic hydrogenolysis.

Benzyl esters of penicillins were previously prepared by the reactions of penicillins in the acid form with phenyldiazomethane.[7] This procedure was tedious as well as hazardous on a large scale. We have prepared the benzyl esters of benzylpenicillin (IIa) and phenoxymethylpenicillin (IIb) in 85% yields by the reactions of the potassium salts Ia and Ib with benzyl bromide in dimethylformamide. Oxidation of IIa and IIb with potassium permanganate in 80% acetic acid gave 42% and 65% yields, respectively, of the corresponding sulfones (IIIa and IIIb). Hydrogenolysis of IIIa and IIIb gave the penicillin sulfones as their free acids (Va and Vb). Oxidation of IIa with hydrogen peroxide did not lead to the expected sulfoxide. This oxidation was readily accomplished, however, by the use of sodium metaperiodate in dioxane to give IVa. After prolonged reaction time with sodium metaperiodate, IIb was oxidized to the sulfoxide benzyl ester IVb. Removal of the benzyl group from IVa and IVb by hydrogenation with 10% palladium-on-charcoal in ethyl acetate gave the expected penicillin sulfoxides as free acids (VIa and VIb).

The presence of a β-lactam ring in the benzyl esters of benzylpenicillin sulfoxide and sulfone, phenoxymethylpenicillin sulfoxide and sulfone as well as their free acids was established by their infrared spectra which show a strong band between 5.5 μ and 5.6 μ, a shift of about 0.05 λ from their unoxidized precursors. This is in accordance with observations by other investigators.

(1) H. T. Clarke, J. R. Johnson, and R. Robinson, ed., "The Chemistry of Penicillin," University Press, Princeton, N. J., 1949, p. 152.

(2) H. T. Clarke, J. R. Johnson, and R. Robinson, ed., "The Chemistry of Penicillin," University Press, Princeton, N. J., 1949, p. 156.

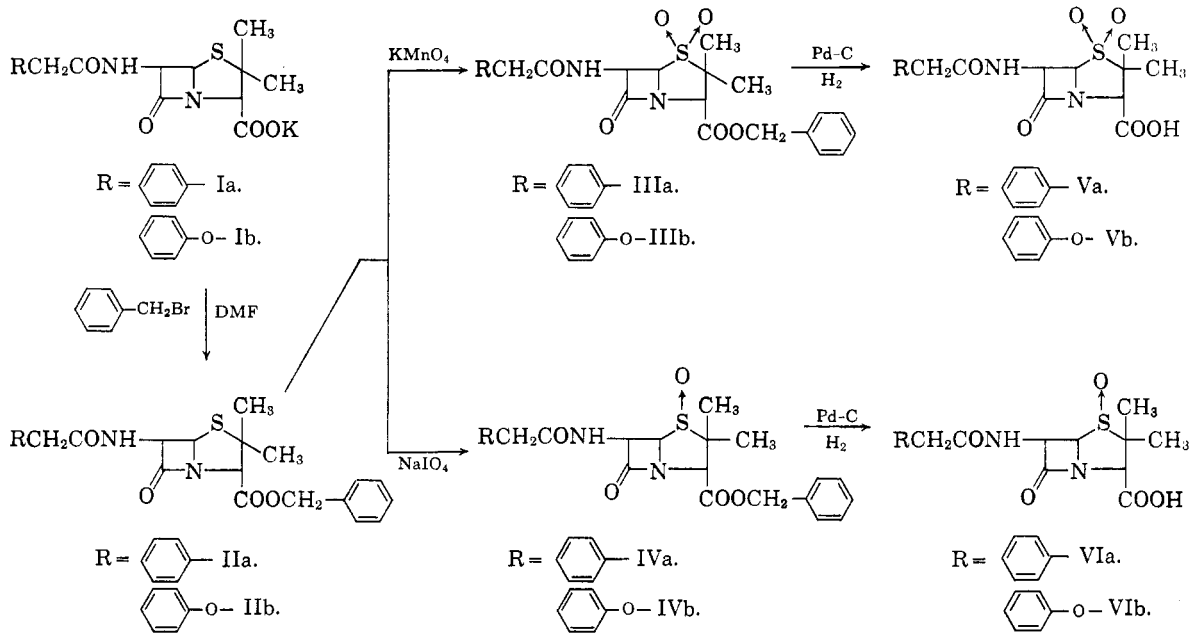
(3) H. T. Clarke, J. R. Johnson, and R. Robinson, ed., "The Chemistry of Penicillin," University Press, Princeton, N. J., 1949, p. 687.

(4) E. F. Rogers and K. Folkers, U. S. Patent **2,483,235** (1949).

(5) K. Meyer, G. L. Hobby, and E. Chaffee, *Science*, **97**, 205 (1943).

(6) A. P. Richardson, H. A. Walker, I. Miller, and R. Hansen, *Proc. Soc. Exp. Biol. and Med.*, **60**, 272 (1945).

(7) H. T. Clarke, J. R. Johnson, and R. Robinson, ed., "The Chemistry of Penicillin," University Press, Princeton, N. J., 1949, p. 93.



EXPERIMENTAL

Benzylpenicillin benzyl ester (IIa). A suspension of 11.16 g. (0.3 mole) of penicillin G potassium salt in 500 ml. of freshly distilled dimethylformamide and 59.8 g. (0.35 mole) of freshly distilled benzyl bromide was stirred at room temperature for 90 min. The mixture was filtered and the filtrate was poured into 1.5 l. of ice water. The resulting oil was extracted into ether, washed with aqueous sodium bicarbonate, and dried over anhydrous sodium sulfate. The dried solution was poured into excess petroleum ether, and the oil which separated was taken up in ether and again dried over sodium sulfate. Evaporation of the ether filtrate *in vacuo* gave 107 g. (84%) of benzylpenicillin benzyl ester as a sirup. The benzyl ester was identified by its infrared spectrum [maxima at 2.98 μ (NH band), 5.60 μ (β-lactam band) and 5.70 μ (ester carbonyl band)], physical and chemical properties, as well as by its behavior in the subsequent chemical operations described below. It was used without further purification.

Phenoxymethylpenicillin benzyl ester (IIb). Using the preceeding procedure, 13.2 g. (0.034 mole) of phenoxymethylpenicillin potassium salt was treated with 6.5 g. (0.038 mole) of benzyl bromide in 500 ml. of dimethylformamide to give, after 3 hr., 12.5 g. (83%) of phenoxymethyl penicillin benzyl ester as a pale yellow oil.

Pertinent infrared bands include: 2.90 (NH), 5.70 (β-lactam), 5.75 (ester carbonyl band), and 5.93 (amide carbonyl band). This compound was likewise used without further purification.

Benzylpenicillin sulfone benzyl ester (IIIa). Benzylpenicillin benzyl ester (IIa), 26 g. (0.06 mole), was dissolved in 400 ml. of 80% acetic acid. To this solution, 21 g. of potassium permanganate in 200 ml. of water was added during a 0.5-hr. period. After another hour, 30% hydrogen peroxide was added in a quantity sufficient to discharge the color. This was followed by 1 l. of water. The oily precipitate which separated was taken up in 80% acetic acid and reprecipitated by addition of three volumes of water. The supernatant liquid was decanted and the gummy precipitate was dissolved in benzene and evaporated to dryness *in vacuo*. Several evaporations with benzene gave an amorphous solid, 11.6 g. (42%) of IIIa.

Anal. Calcd. for $C_{23}H_{24}N_2O_6S$: C, 60.51; H, 5.30; N, 6.14. Found: C, 60.79; H, 5.53; N, 6.25.

Phenoxymethylpenicillin sulfone benzyl ester (IIIb). Phenoxymethylpenicillin benzyl ester (IIb), 12.5 g. (0.0284 mole), was oxidized in a manner similar to that used for the benzyl analog.

The gummy product obtained was taken up in chloroform, washed twice with 5% sodium bicarbonate, twice with water, and dried over sodium sulfate. Removal of the drying agent and solvent left 12.5 g. of a gummy material which was crystallized from benzene–petroleum ether (b.p. 30–60°); yield 8.7 g. (65%), m.p. 124–125°.

Anal. Calcd. for $C_{23}H_{24}N_2O_7S$: C, 58.46; H, 5.12; N, 5.93. Found: C, 58.46; H, 5.26; N, 5.79.

Benzylpenicillin sulfone (Va). A solution of 6.85 g. (0.015 mole) of benzylpenicillin sulfone benzyl ester (IIIa) in 200 ml. of methanol was subjected to hydrogenation at 50 p.s.i. in the presence of 5.5 g. of 10% palladium-on-carbon which had been prehydrogenated for 15 min. The hydrogen uptake was completed in 30 min., and the mixture was filtered and concentrated to give 2.5 g. of crude Va. The crude product was extracted with *n*-butyl acetate, and the extract was concentrated to a yellow solid. Two recrystallizations from ethyl acetate–petroleum ether (1:2) yielded 1.43 g. (26%) of crystalline solid, m.p. 121–122° (with dec.).

Anal. Calcd. for $C_{16}H_{18}N_2O_6S$: C, 52.45; H, 4.95; N, 7.65. Found: C, 52.61; H, 5.41 N, 7.38.

Phenoxymethylpenicillin sulfone (Vb). A solution of 0.945 g. (0.002 mole) of phenoxymethylpenicillin sulfone benzyl ester (IIIb) in 100 ml. of dry ethyl acetate was hydrogenated at atmospheric pressure with 1.5 g. of prereduced 10% palladium-on-charcoal. The reaction was complete in 15 min., and the crude product was crystallized from ether–hexane; yield, 0.38 g. (50%), m.p. 147° (with dec.).

Anal. Calcd. for $C_{16}H_{18}N_2O_7S \cdot H_2O$: C, 48.00; H, 5.03. Found: C, 48.17; H, 5.37.

Benzylpenicillin sulfoxide benzyl ester (IVa). A stirred solution of 9.1 g. (0.0214 mole) of benzylpenicillin benzyl ester (IIa), in 860 ml. of dioxane and 515 ml. of *p*H 6.8 phosphate buffer was treated with 310 ml. of a 0.25 M sodium periodate solution and then stirred for 1 hr. The resulting solution was concentrated to 300 ml. at low temperature and the oil which separated was extracted into chloroform. The chloroform extract was dried and concentrated to an oil which crystallized upon the addition of ether. The crude product (3.15 g., m.p. 139–145°) was recrystallized from ethyl acetate–petroleum ether to give 2.6 g. (27%) of colorless crystals, m.p. 146–148°.

Anal. Calcd. for $C_{23}H_{24}N_2O_6S$: C, 62.71; H, 5.49; N, 6.36. Found: C, 62.65; H, 5.60; N, 6.63.

Phenoxymethylpenicillin sulfoxide benzyl ester (IVb). Phenoxymethylpenicillin benzyl ester was much more resistant to oxidation with sodium periodate. A solution of 4.7 g. (0.0107 mole) of phenoxymethylpenicillin benzyl ester IIb was stirred with sodium periodate in dioxane–phosphate buffer for 10 hr. at room temperature, then for 4 days with fresh sodium periodate–dioxane–phosphate buffer, and finally for 2 days at 50° with fresh periodate–dioxane–phosphate buffer. The reaction mixture was worked up as with the benzylpenicillin sulfoxide benzyl ester. Evaporation of the chloroform solution gave an oil which crystallized after 9 days to give 2.95 g. (61%) of crude phenoxymethylpenicillin sulfoxide benzyl ester IVb, m.p. 123–125°. Recrystallization from ethyl acetate–petroleum ether gave 2.75 g. (57%) of crystalline solid, m.p. 124–125°.

Anal. Calcd. for $C_{23}H_{24}N_2O_6S$: C, 60.51; H, 5.30; N, 6.14. Found: C, 60.44; H, 5.84; N, 6.52.

Benzylpenicillin sulfoxide (VIa). Benzylpenicillin sulfoxide benzyl ester IVa, 1.76 g. (0.004 mole), was hydrogenated at atmospheric pressure with 2.6 g. of pre-reduced 10% palladium on charcoal in dry ethyl acetate. The reaction was completed in 0.5 hr. After filtering off the catalyst, the filtrate was evaporated *in vacuo* to a solid which was crystallized from ethyl acetate–petroleum ether to give 1.02 g. (73%) of product, m.p. 142–143° (with dec.).

Anal. Calcd. for $C_{16}H_{18}N_2O_5S$: C, 54.84; H, 5.18; N, 8.00. Found: C, 55.13; H, 5.28; N, 8.26.

Phenoxymethylpenicillin sulfoxide (VIb). In a similar manner 0.913 g. (0.002 mole) of phenoxymethylpenicillin sulfoxide benzyl ester (IVb) was hydrogenated to give 0.582 g. (79%) of colorless crystalline solid after recrystallization from ethyl acetate–petroleum ether, m.p. 167–168° (with dec.).

Anal. Calcd. for $C_{16}H_{18}N_2O_6S$: C, 52.45; H, 4.95; N, 7.65. Found: C, 52.42; H, 4.92; N, 7.93.

Acknowledgment. We are indebted to Mrs. D. Rolston and associates for the elemental analyses.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

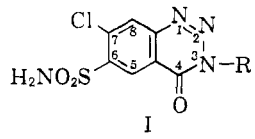
1,2,3-Benzotriazine Sulfonamides. A New Class of Oral Diuretic Agents[1]

SHREEKRISHNA M. GADEKAR AND JEAN L. FREDERICK

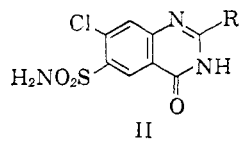
Received November 20, 1961

A series of 7-chloro-6-sulfamyl-1,2,3-benzotriazine-4(3*H*)-ones have been prepared from *N*-acetyl-4-chloro-5-sulfamylanthranilic acid. Some of these compounds possess diuretic activity.

During a continuing search, in these laboratories, for a better, orally active diuretic agent, we had the opportunity to examine a series of 7-chloro-6-sulfamyl-1,2,3-benzotriazine-4(3*H*)-ones (I).



I



II

On oral administration these compounds, like the quinazolinone sulfonamides[2] (II) and the chlorothiazide and hydrochlorothiazide,[3,4] types of diuretic agents, caused a pronounced natriuresis and chloruresis in experimental animals, but at the same time showed only a relatively small increase in potassium excretion.[5] Structurally they might be considered nitrogen isosteres of the quinazolinone sulfonamides II, which have been reported to be active diuretic agents. Thus, it becomes apparent that the replacement of carbon, at the 2- position, with nitrogen in the quinazolinone sulfonamide series does not cause a loss of biological activity. Substitution of hydrogen at position 3 with amino or lower alkyl groups, such as methyl and ethyl, resulted in decreased activity. A complete loss of activity occurred when this position was occupied by a benzyl or β-dimethylaminoethyl group.

The starting material for the syntheses, namely, *N*-acetyl-4-chloro-5-sulfamylanthranilic acid, has been described.[2] When this was esterified with methanol and sulfuric acid, a simultaneous loss of the acetyl group occurred, and methyl 4-chloro-5-sulfamylanthranilate (III) was obtained in 49% yield. Treatment of the ester with concentrated ammonium hydroxide at room temperature for seventy-two hours afforded the anthranilamide. When aqueous solutions of other amines were used in place of ammonia, corresponding substituted amides were formed as summarized in Table I.

Diazotizations of the amino amides with nitrous acid gave the 7-chloro-6-sulfamyl-1,2,3-benzotriazine-4(3*H*)-ones as shown in Table II.

The benzyl analog XII was prepared by diazotizing III, neutralizing the excess mineral acid with sodium hydroxide, and treating the diazo solution with benzylamine. A similar procedure has been used by Van Heyningen[6] for the syntheses

(1) Presented before the Division of Medicinal Chemistry at the 138th Meeting of the American Chemical Society, New York, September 1960.

(2) E. Cohen, B. Klarberg, and J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **81**, 5508 (1959).

(3) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957).

(4) G. De Stevens, L. H. Werner, A. Halamandaris, and S. Ricca, Jr., *Exper.*, **14**, 463 (1958).

(5) The information on the pharmacology of these compounds was kindly furnished by Dr. J. R. Cummings and his associates, Department of Pharmacology, Experimental Therapeutics Section, Pearl River Laboratories, N. Y.

(6) E. Van Heyningen, *J. Am. Chem. Soc.*, **77**, 6562 (1955).