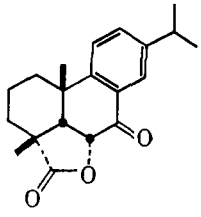
ture V.[6] The p.m.r. spectrum of the 7-acetoxylactone, obtained on acetylation of the hydroxylactone, showed a C-5-H doublet at 2.43 p.p.m. (J = 7.0 c.p.s.), a C-6-H quartet at 5.15 p.p.m. (J = 7.0, 2.5 c.p.s.), and a C-7-H multiplet at 6.29 p.p.m. ($J_{6,7}$ = 2.5 c.p.s.), characteristic of structure IVb. Hence its precursor possesses structure IVa.



V

Thus, all reduction products appear to be 5-iso compounds, as might be expected from an initial methanolytic ring opening of the lactone I, followed by borohydride reduction of the resultant 5-iso-6,7-dione. The rapid formation of a yellow color in the methanolic solution of I upon borohydride addition is consistent with this view. The low yield of reduction product may be due to much enol–acid–borohydride complex formation.

Experimental Section

5-Isodehydroabietic Acid. A.—A mixture of 28 mg. of lactone III, 3 g. of amalgamated zinc, 2 ml. of acetic acid, and 6 ml. of 6 *N* hydrochloric acid was refluxed for 50 hr. The mixture was cooled, decanted, and extracted with ether. The extract was washed with 5% sodium hydroxide, the aqueous extract acidified and extracted with ether. The organic extract was dried over magnesium sulfate and evaporated. The residue (16 mg.) was crystallized from aqueous methanol yielding the acid II, m.p. 121–124° (lit.[3] m.p. 121–124°); the infrared spectrum was identical with that of an authentic specimen.

B.—Calcium (15 mg.) was added to a solution of 35 mg. of ketolactone V in 5 ml. of tetrahydrofuran and 30 ml. of liquid ammonia. Upon dissolution of the metal, 200 mg. of ammonium sulfate was added and the mixture was evaporated. Addition of 5% hydrochloric acid, extraction with chloroform, and evaporation of the extract yielded 30 mg. of solid. A mixture of the latter, 5 drops of concentrated sulfuric acid, and 45 mg. of 10% palladium–charcoal in 15 ml. of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. Upon filtration of the catalyst the solution was washed with water and evaporated. Sublimation of the residue yielded 15 mg. of II, m.p. and m.m.p. 123–124°; its spectra were identical with those of an authentic sample.

Hydroxylactone IVa.—A solution of 200 mg. of lactone I and 100 mg. of sodium borohydride in 25 ml. of methanol was left standing for 30 min. and then evaporated under reduced pressure. Water was added to the residue and the solution was extracted with ether. The extract was dried over anhydrous sodium sulfate and evaporated. Trituration of the residue with ether yielded crystals whose sublimation gave 20 mg. of lactone IVa, m.p. 238°; spectra—infrared (Nujol), OH 2.82 (m), C=O 5.67 (s) μ; p.m.r., three-proton singlets at 0.98, 1.31 (4- and 10-methyls, respectively), three-proton doublets at 1.13, 1.18 (J = 7 c.p.s.) (isopropyl methyls), one-proton doublet at 2.45 (J = 6.5 c.p.s.) [C-5-H], one-proton quartet at 5.08 (J = 6.5, 2.5 c.p.s.) [C-6-H], one-proton doublet at 5.28 p.p.m. (J = 2.5 c.p.s.) [C-7-H]. *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.28; H, 8.34.

Acetoxylactone IVb.—A solution of 30 mg. of lactone IVa in 1 ml. of acetic anhydride and 1 ml. of pyridine was heated for 3 hr. on the steam bath. Upon evaporation of the solution under vacuum, the residue was extracted with ether. Evaporation of the extract and crystallization of the residue from petroleum ether (b.p. 30–60°) gave 32 mg. of crystalline lactone IVb, m.p. 152–153°; spectra—infrared (CCl_4), C=O 5.62 (s), 5.74 (s) μ; p.m.r., three-proton lines at 1.17, 1.18, 1.30, and 1.31 (4-, 10- and isopropropyl methyls), and three-proton singlet at 2.30 p.p.m. (acetate methyl). *Anal.* Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.03; H, 7.86.

Ketolactone V.—Jones reagent (2 ml.) was added rapidly to an ice-cold solution of 61 mg. of lactone IVa in 25 ml. of acetone, and the mixture was stirred for 4 min. It was poured onto ice and extracted with chloroform. The extract was washed with water, 5% sodium bicarbonate solution, and again with water. Evaporation of the organic solution yielded 54 mg. of solid whose crystallization from ether gave long needles of lactone V: m.p. 128°; spectra—ultraviolet (95% EtOH), λ_{max} 255 mμ (log ϵ 3.92), 300 mμ (log ϵ 3.23), λ_{min} 233 mμ (log ϵ 3.45), 285 mμ (log ϵ 3.15); infrared (Nujol), C=O 5.65 (s), 5.85 (s), C=C 6.21 (m) μ; p.m.r., three-proton singlets at 1.29, 1.43 (4- and 10-methyls), six-proton doublet at 1.36 p.p.m. (J = 7.0 c.p.s.) (isopropyl methyls). *Anal.* Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.97; H, 7.71.

Sodium borohydride, 15 mg., was added in small portions to a solution of 30 mg. of the lactone V in 5 ml. of methanol and the mixture was left standing for 30 min. at room temperature. Water and 5% hydrochloric acid were added and the mixture was extracted with chloroform. Evaporation of the solvent yielded 30 mg. of crystalline IVa, m.p. and m.m.p. 238°; the spectra were identical with those of an authentic sample.

(6) A Dreiding model of V reveals that one of the conformers of this all-*cis* bridgehead arrangement forces the 7-keto function out of coplanarity with the benzene ring without introducing undue extra strain into the ring system. This may be the stable conformation and account for the unusual spectral properties of the aromatic ketone: an infrared carbonyl stretching band of too low a wave length, an abnormally low-intensity infrared C=C stretching band, and a major ultraviolet absoption peak of anomalously low intensity (see the Experimental Section).

Penicillin Sulfoxides

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The sulfoxides of benzylpenicillin and phenoxymethylpenicillin have been prepared by esterification of the carboxyl function followed by oxidation with sodium metaperiodate[1] or hydrogen peroxide,[2] and subsequent removal of the protecting group by hydrogenolysis. We wish to report a general procedure for the *direct* preparation of penicillin sulfoxides. Using sodium metaperiodate in aqueous solution at pH 6.5–7.0 we have obtained the sulfoxides of phenoxymethylpenicillin, (5-methyl-3-phenyl-4-isoxazolyl)penicillin (oxacillin[3]), D-(−)-α-aminobenzylpenicillin (ampicillin[3]), 6-N-carbobenzyloxyaminopenicillanic acid, 6-phthalimidopenicillanic acid, 6-triphenylmethylaminopenicillanic acid, and 6-aminopenicillanic acid by direct oxidation of their salts or free acids. Ampicillin was also oxidized as its N-carbobenzyloxy derivative, and the protecting group was then removed by hydrogenolysis. The sulfoxides were characterized by elemental analyses and by their infrared spectra (KBr disk). A weak-to-medium intensity band due to the S→O stretching

(1) A. W. Chow, N. M. Hall, and J. R. E. Hoover, *J. Org. Chem.*, **27**, 1381 (1962).

(2) E. Guddal, P. Morch, and L. Tybring, *Tetrahedron Letters*, **No. 9**, 381 (1962).

(3) The trademarks of Bristol Laboratories, a division of Bristol-Myers Co., for oxacillin and ampicillin are, respectively, Prostaphlin and Polycillin.

TABLE I
PENICILLIN SULFOXIDES

Sulfoxide	Formula	Yield, %	M.p., °C. dec.	Isolation method	Calcd. % C	Calcd. % H	Found % C	Found % H
Phenoxymethylpenicillin	$C_{16}H_{18}N_2O_6S$	76	178–180[a]	a	52.45	4.95	52.66	5.18
(5-Methyl-3-phenyl-4-isoxazolyl)-penicillin (sodium salt hemihydrate)	$(C_{19}H_{18}NaN_3O_6S)_2 \cdot H_2O$	36	165–167	b	50.89	4.27	51.03	4.59
D-(−)-α-N-Carbobenzyloxyaminobenzylpenicillin hemihydrate	$(C_{24}H_{25}N_3O_7S)_2 \cdot H_2O$	52	133–135	a	56.70	5.16	56.25	5.32
D-(−)-α-Aminobenzylpenicillin dihydrate	$C_{16}H_{19}N_3O_5S \cdot 2H_2O$	25	210–212	c	47.88	5.78	48.15	5.78
6-Phthalimidopenicillanic acid hemihydrate	$(C_{16}H_{14}N_2O_6S)_2 \cdot H_2O$	35	160–162	a	51.75	4.07	51.37	4.22
6-Aminopenicillanic acid sesquihydrate	$(C_8H_{12}N_2O_4S)_2 \cdot 3H_2O$	8	248–250	c	37.06	5.83	37.10	5.57
6-N-Carbobenzyloxyaminopenicillanic acid (potassium salt monohydrate)	$C_{16}H_{17}KN_2O_6S \cdot H_2O$	46	138.5–140	b	45.48	4.53	45.70	4.28
6-Triphenylmethylaminopenicillanic acid (potassium salt hemihydrate)	$(C_{27}H_{25}KN_2O_4S)_2 \cdot H_2O$	88	213–215	b	62.16	5.03	62.29	5.06

[a] Lit.[1] m.p. 167–168° dec.; for the hemihydrate, lit.[2] m.p. 159° dec.

vibration occurred at 1020–1035 cm.$^{-1}$, and the characteristic displacement of the β-lactam carbonyl absorption band to shorter wave length[1,2] was also observed. In the sulfoxides reported here, this displacement varied from 10 to 30 cm.$^{-1}$ relative to the corresponding band in the unoxidized precursors.

Experimental Section[4]

The data on the sulfoxides prepared in this work are recorded in Table I.

General Procedure for the Preparation of Penicillin Sulfoxides.—A solution of the penicillin salt or free acid (0.10 mole) in the minimum volume of water at pH 7.5–8.0 was added to a solution of 23.5 g. (0.11 mole) of sodium metaperiodate in 750 ml. of water. The pH of the mixture was adjusted to 6.5–7.0 and maintained at this value while the solution was stirred at room temperature for 2.5 hr. The pH was then lowered to 2–2.5 by addition of 40% phosphoric acid and the product was isolated in one of the following three ways. (a) The precipitated sulfoxide was collected, thoroughly washed with cold water, dried by suction, and recrystallized from an acetone–water mixture. (b) The gummy solid which separated was extracted into ethyl acetate, and the washed and dried extract was treated with 1 molar equiv. of a 50% solution of either potassium or sodium 2-ethylhexanoate in 1-butanol. The alkali metal salt thus obtained was collected and was recrystallized from a 1-butanol–water mixture. (c) The acidic aqueous solution was extracted with a solution of 600 ml. of methyl isobutyl ketone containing 33.3 g. (0.075 mole) of dioctyl sodium sulfosuccinate (Aerosol OT). The organic phase was dried briefly over magnesium sulfate and then was treated dropwise with triethylamine to pH 5.0. The amorphous product which precipitated was collected and dried *in vacuo*.

D-(−)-α-Aminobenzylpenicillin Sulfoxide.—D-(−)-α-N-Carbobenzyloxyaminobenzylpenicillin sulfoxide (2 g.) was dissolved in 100 ml. of 1% sodium bicarbonate solution. This solution was shaken in an atmosphere of hydrogen under an initial pressure of 45 p.s.i.g. for 2 hr. in the presence of 2 g. of 30% palladium on diatomaceous earth catalyst. The mixture was acidified to pH 2 with 6 *N* hydrochloric acid and filtered through diatomaceous earth (Dicalite). The pH of the filtrate was adjusted to 4.65, and the clear solution was concentrated under reduced pressure at 33° to a volume of 20 ml. On cooling, the sulfoxide of D-(−)-α-aminobenzylpenicillin separated and was collected and dried *in vacuo* over phosphorus pentoxide. The infrared and n.m.r. spectra of this product were identical with those obtained from the sample formed by direct oxidation of D-(−)-α-aminobenzylpenicillin.

(4) Melting points were determined either on a Kofler hot stage, a Fisher-Johns apparatus, or in open capillaries, and are all corrected. We thank Mr. R. M. Downing and Mrs. C. Kalinowski for the microanalyses, and Messrs. D. Whitehead and A. Vulcano for infrared and n.m.r. spectral measurements.

1,2-Diphenyl-3-nitrocyclopropene or 2,3-Diphenyl-2-cyclopropenyl Nitrite[1]

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In our endeavors to synthesize potential diazocyclopropene precursors, we had occasion to attempt to nitrosate N,N-dimethyl-N′-(2,3-diphenyl-2-cyclopropenyl)urea (I). The successful method employing a modification of the technique developed by White[3] and his group in which the urea was treated with dinitrogen tetroxide at low temperature (−55°) has already been reported.[4]

However, in the earlier stages of this research, we attempted to nitrosate this material in another method developed by White[3] which employs sodium nitrite in a mixture of acetic acid and acetic anhydride. Under these conditions and using a rather large excess of the sodium nitrite, a new white compound was formed in 67% yield which gave the correct analysis for a nitro or a nitrite derivative of 1,2-diphenylcyclopropene. Since the nitro derivative would be quite interesting for a variety of reasons including its potential as a cyclopropenyl carbanion precursor, its an-

(1) Taken from a thesis submitted by John W. Kobzina in partial fulfillment of the requirements for the degree of Master of Science at the University of Florida.

(2) Alfred P. Sloan Fellow.

(3) *Cf.* E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955). For more recent developments in nitrosation procedures, see E. H. White and F. W. Bachelor, *Tetrahedron Letters*, 77 (1965), and references cited therein.

(4) W. M. Jones and J. M. Denham, *J. Am. Chem. Soc.*, **86**, 944 (1964).