gen bromide. The solution was kept 2 hr. at 25°, poured into 1 l. of dry ether, and the precipitate removed, washed with ether, and dried *in vacuo*. The resulting crude hydrobromide salt of the tetrapeptide, 9 g., was dissolved in 50 ml. of dimethylformamide, cooled to 0°, and 4 g. of triethylamine added. After 5 min., the solid was removed and 4.5 g. (0.0107 mole) of carbobenzoxy-L-phenylalanine *p*-nitrophenyl ester was added to the filtrate. The yellow solution was stirred 18 hr. at 25°, diluted with 250 ml. of ethyl acetate; the solution was washed with water, aqueous 5% sodium carbonate, water, and dilute hydrochloric acid. The solution was dried over magnesium sulfate, evaporated to a small volume, and ether added. The solid was removed and recrystallized from dimethylformamide–ether; yield 5 g. (50%), m.p. 215–216°, $[\alpha]^{23}D$ −60° (*c* 1.1, dimethylformamide); reported[5] m.p. 214–216°, $[\alpha]^{20}D$ −57° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{43}H_{53}N_9O_{12}$: C, 58.17; H, 6.02; N, 14.20; O-Ac, 4.85. Found: C, 58.10; H, 6.17; N, 14.29; O-Ac, 4.55.

Carbobenzoxyglycyl-L-phenylalanyl-O-acetyl-L-seryl-L-prolyl-L-phenylalanylnitro-L-arginine Methyl Ester.—The carbobenzoxy group was removed from 3.5 g. (0.004 mole) of the pentapeptide with hydrobromic acid–acetic acid. The crude product was dissolved in 50 ml. of dimethylformamide, cooled to 5°, and 1 g. of triethylamine added. The precipitate was removed and 1.5 g. (0.0045 mole) of carbobenzoxyglycine *p*-nitrophenyl ester was added to the filtrate. After 3 days at room temperature, the solution was diluted with four volumes of ethyl acetate giving a white solid which was recrystallized from methanol–ether; 3 g. (79%), m.p. 222–224°, $[\alpha]^{23}D$ −55.8° (*c* 1, dimethylformamide).

Anal. Calcd. for $C_{45}H_{56}N_{10}O_{13}$: C, 57.20; H, 5.97; N, 14.83; O-Ac, 4.56. Found: C, 57.19; H, 5.96; N, 14.92; O-Ac, 4.20.

Penicillin Sulfones

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We wish to report an improved procedure for preparing penicillin sulfones. Recent syntheses[1,2] have required that the carboxyl group be esterified during oxidation, and the protecting group be subsequently removed by hydrogenolysis. Using potassium permanganate in neutral aqueous solution, we prepared the sulfones of benzylpenicillin, 2,6-dimethoxyphenylpenicillin (methicillin[3]), 5-methyl-3-phenyl-4-isoxazolylpenicillin (oxacillin[3]), D-(−)-α-aminobenzylpenicillin (ampicillin[3]), and *dl*-α-phenoxyethylpenicillin (phenethicillin[3]) by direct oxidation of their salts or free acids. Ampicillin was oxidized as its N-carbobenzyloxy derivative which yielded ampicillin sulfone on hydrogenolysis.

The products were easily isolated and purified in satisfactory yields. Infrared spectra of the sulfones showed the characteristic shift of the β-lactam band from 5.6 to 5.50–5.53 μ, and the appearance of bands at 7.6 and 8.9 μ due to the sulfone group.

Experimental[4]

The sulfones prepared in this work, their physical constants, elemental analyses, and other data are listed in Table I.

General Procedure for the Preparation of Penicillin Sulfones.—The appropriate penicillin salt or free acid (0.035 mole) was added to 180 ml. of water, the pH was adjusted to 7.0–7.5, and the resulting solution was cooled to 0–5°. A solution of 5.5 g. (0.035 mole) of potassium permanganate, 1.80 ml. of 85% phosphoric acid (specific gravity 1.70), and 140 ml. of water was added to the penicillin solution at such a rate as to keep the temperature below 10°. The pH was maintained between 6.0 and 7.5 using 5–10% aqueous sodium hydroxide or 10% phosphoric acid. About 10 min. after the addition, excess potassium permanganate was destroyed with sodium bisulfite, if necessary. The manganese dioxide was removed by passing the mixture through a Dicalite-precoated filter, and the pH of the cooled filtrate was then slowly adjusted to 2.0–2.3 with 10% phosphoric acid. The penicillin sulfone-free acid which precipitated was collected and washed with cold water. It was usually dried by storing overnight in a vacuum desiccator over Drierite.

Two compounds needing special comment are described.

D(−)-α-Aminobenzylpenicillin Sulfone.—D(−)-α-N-Carbobenzyloxyaminobenzylpenicillin sulfone, 7.5 g. (0.0146 mole) was added to 70 ml. of water and dissolved by adjusting the pH to 6.5 with 10% sodium hydroxide. The previous solution was added to 7.5 g. of prehydrogenated 30% palladium-on-diatomaceous earth catalyst in 25 ml. of water and shaken under 48 p.s.i.g. of hydrogen for 2.25 hr. Methyl isobutyl ketone (50 ml.) was added, the

(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*, **9**, 381 (1962).

(3) The trade-marks of Bristol Laboratories, a division of Bristol-Myers Co., for methicillin, oxacillin, ampicillin, and phenethicillin are, respectively, Staphcillin, Prostaphlin, Polycillin, and Syncillin.

(4) All melting points are corrected. Microanalyses were performed by Richard M. Downing, and the infrared measurements were performed by David F. Whitehead.

TABLE I

PENICILLIN SULFONE FREE ACIDS

Penicillin sulfone	Molecular formula	Yield, %	M.p., °C. dec.	Recrystallization solvent	Analyses—Calcd. % C	Analyses—Calcd. % H	Analyses—Found % C	Analyses—Found % H
Benzyl	$C_{16}H_{18}N_2O_6S$	84–87	123.0–124.0	Ethyl acetate and petroleum ether	52.46	4.95	52.70	5.14
2,6-Dimethoxyphenyl	$C_{17}H_{20}N_2O_8S$	55–70	174.5–174.8	Ethyl acetate and petroleum ether	49.51	4.89	49.45	5.30
5-Methyl-3-phenyl-4-isoxazolyl	$C_{19}H_{19}N_3O_7S$	35–61	132.0–134.0	Water	52.65	4.42	52.74	4.49
D-(−)-α-N-Carbobenzyloxyaminobenzyl-hemihydrate[a]	$(C_{24}H_{25}N_3O_8S)_2H_2O$	30–42	115.0–116.5	Ethyl acetate and petroleum ether	55.00	4.99	55.20	4.67
D-(−)-α-Aminobenzyl	$C_{16}H_{19}N_3O_6S$	30	228.6–229.4	Aerosol OT-methyl isobutyl ketone	50.39	5.02	50.80	5.05
dl-α-Phenoxyethyl(*sym*-dibenzylethylenediamine salt)	$C_{60}H_{60}N_6O_{14}S_2$	60	118.0–118.3	Methyl isobutyl ketone	58.05	5.81	57.70	5.86

[a] Calcd. for water: 1.7%. Found: 1.6%

pH was adjusted to 2.0, and the mixture was passed through a Dicalite-precoated filter. The aqueous layer was then extracted with 6.5 g. (0.0146 mole) of Aerosol OT in 80 ml. of methyl isobutyl ketone while the temperature was held at 0–5° and the pH held at 2.0. The organic layer was passed through a Dicalite-precoated filter and adjusted to a pH of 5.8 with triethylamine. Crystals of D-(−)-α-aminobenzylpenicillin sulfone separated. After stirring cold for 10 min. they were collected by filtration, washed with petroleum ether (b.p. 60–70°), and dried.

N,N'-Dibenzylethylenediamine Di-*dl*-α-phenoxyethylpenicillinate Sulfone.—This sulfone was prepared by the general procedure described before with these exceptions. The aqueous solution, after the manganese dioxide was removed, was mixed with 300 ml. of methyl isobutyl ketone, and the pH was adjusted to 2.0 with 10% phosphoric acid. The organic layer was dried over anhydrous sodium sulfate and, after the drying agent was removed, was treated with 4.2 g. (0.018 mole) of *sym*-dibenzylethylenediamine. The crystalline dibenzylethylenediamine salt of *dl*-α-phenoxyethylpenicillin sulfone precipitated almost immediately. After stirring cold for 1 hr., the mixture was filtered, washed with methyl isobutyl ketone and petroleum ether (b.p. 60–70°), and dried.

Synthesis of Trimethylhydroquinone

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It is known that tocopherols (vitamin E) are synthesized by condensation of trimethylhydroquinone with phytol[1] or its derivatives.[2–5]

Trimethylhydroquinone is an important starting material in synthesizing tocopherol. A number of investigations on the synthesis of trimethylhydroquinone have been carried out with 2,3,5-trimethylbenzene,[6] 2,3,5-trimethylphenol,[7] and 3,5-dimethylphenol[8] as the starting material.

Recently Burke[9] succeeded in a synthesis of trimethylhydroquinone from 4-benzyloxyphenol.

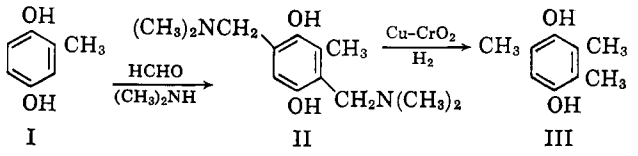
Caldwell and Thompson[8] prepared 3,5-dimethyl-2-dimethylaminomethylphenol by the condensation of 3,5-dimethylphenol with dimethylamine and formaldehyde, which was then converted into 2,3,5-trimethylphenol.

They also prepared 2,5-dimethylhydroquinone from 2,5-bis(dimethylaminomethyl)hydroquinone, obtained in the condensation of hydroquinone with dimethylamine and formaldehyde. However, efforts to obtain the required tris(dimethylaminomethyl)hydroquinone were not successful.

A new way of synthesizing trimethylhydroquinone presented in this paper comprises only two steps from 2-methylhydroquinone, which is the smallest in number ever attained in any procedures so far reported.

This investigation was carried out independently of the synthesis of trimethylhydroquinone from 4-benzyloxyphenol by Burke and co-workers.[9]

The conversion of 2-methylhydroquinone into trimethylhydroquinone involves the following steps.



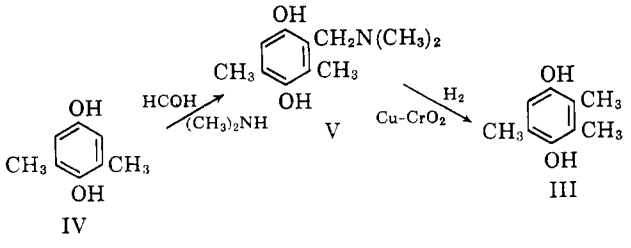
I II III

2-Methylhydroquinone (I) reacts smoothly with dimethylamine and formaldehyde to give 2-methyl-3,6-bis(dimethylaminomethyl)hydroquinone (II) in 72% yield.

The di-Mannich base (II), recrystallized from ether as colorless needles, is very unstable and upon heating or even exposure to air for a long time, polymerized to a dark brown sticky mass.

The base (II) was hydrogenolyzed in the presence of copper chromium oxide in dioxane at 180° under a pressure of about 140 atm. of hydrogen to trimethylhydroquinone (III) in 58% yield. From the fact that the base (II) shows a sharp melting point (97–99°) and no characteristic absorption band for the free phenolic group in the infrared spectrum, the position of the dimethylaminomethyl groups must be 3,6- or 5,6- and not a mixture, and from the point of the spacial effect it may be the 3,6-disubstituted compound as shown in II.

Similarly, 3,5-dimethylhydroquinone is converted into trimethylhydroquinone.



IV III

The condensation of 3,5-dimethylhydroquinone (IV) with dimethylamine and formaldehyde in dioxane under mild conditions gives 3,5-dimethyl-2-dimethylaminomethylhydroquinone (V) in 75% yield.

The hydrogenolysis of the mono-Mannich base (V) in dioxane gives trimethylhydroquinone (III) in 60% yield.

This represents a new and more practical synthesis of trimethylhydroquinone.

Experimental[10]

2-Methyl-3,6-bis(dimethylaminomethyl)hydroquinone (II).—To a solution of recrystallized 2-methylhydroquinone (I, 5.0 g.,

(1) P. Karrer, H. Salmon, and H. Fritzshe, *Helv. Chim. Acta*, **21**, 309 (1938); Hoffmann-La Roche and Co., Swiss Patent 212,353 (1941); P. Karrer and O. Isler, U. S. Patent 2,411,968 (1946); O. Ehrman, German Patent 1,015,446 (1958).

(2) Hoffman-La Roche and Co., Swiss Patent 208,446 (1940); P. Karrer and O. Isler, U. S. Patent 2,411,969 (1946).

(3) P. Karrer, R. Esher, H. Fritzsche, K. Keller, B. Ringier, and H. Salmon, *Helv. Chim. Acta*, **21**, 939 (1938); P. Karrer and H. Keller, *ibid.*, **21**, 1161 (1938); J. D. Surmatis and J. Weber, U. S. Patent 2,723,278 (1955); J. D. Surmatis and J. Weber, Canadian Patent 530,254 (1956).

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(6) L. I. Smith, J. W. Opie, S. Wawzoneck, and W. Prichard, *J. Org. Chem.*, **4**, 318 (1939); A. Pongratz and K. L. Zirm, *Monatsh.*, **83**, 13 (1952); C. K. Hui, *J. Vitaminol.* (Japan), I, 8 (1957); F. L. Grinberg and A. A. Svishchuk, *Ukr. Khim. Zh.*, **23**, 79 (1957).

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(8) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).

(9) W. J. Burke, J. A. Warburton, J. L. Bishop, and J. L. Bilis, *J. Org. Chem.*, **26**, 4669 (1961).

(10) Melting points are uncorrected. Infrared spectra were recorded with a Shimadzu Model AR 275 spectrophotometer.