the reaction conditions but have little effect on the stability of cephalothin. Other factors such as stabilization of the intermediate carbonium ion[7] or change in the polar character of the solvent may be relevant. The proposed mechanism[7] precludes displacement of the acetoxy group by the added ion and subsequent displacement by pyridine.

We have established the generality of the findings described in this paper by applying them to the synthesis of substituted pyridinium derivatives of cephalothin as well as to several other 7-acylaminocephalosporanic acids. The products of this study and their antibacterial activity will be reported.[8]

Experimental Section

Cephaloridine (without Isolation of Salt).—A solution of 200 g (0.46 mole) of cephalothin,[2] 100 g (1.04 moles) of potassium thiocyanate, and 100 ml (1.25 moles) of pyridine in 500 ml of water was adjusted to pH 6.5 with 85% phosphoric acid and was heated with stirring at 60° for 6 hr. After cooling to room temperature, the solution was extracted with 25% Amberlite LA-1 (acetate form)[9] in methyl isobutyl ketone (MIBK) (six 1-l. portions) and washed with MIBK (500 ml). The aqueous solution was allowed to stand overnight in the cold (5°). The product which separated weighed 41 g (20%); $\lambda_{max}^{H_2O}$ 238 mμ (ε 15,200) and 251 mμ (ε 13,950). A sample was block dried at 100° for analysis.

Anal. Calcd for $C_{19}H_{17}N_3O_4S_2$: C, 54.92; H, 4.12; N, 10.11; S, 15.43. Found: C, 54.65; H, 4.36; N, 10.06; S, 14.70.

Cephaloridine Hydrothiocyanate.—A solution of 5.0 g (0.012 mole) of cephaloridine and 2.5 g (0.026 mole) of potassium thiocyanate in 100 ml of water was adjusted to pH 2.0 with 10% hydrochloric acid. The resulting salt weighed 5.2 g (91%); $\lambda_{max}^{H_2O}$ 236 mμ (ε 15,900) and 255 mμ (ε 14,300).

Anal. Calcd for $C_{19}H_{17}N_3O_4S_2 \cdot HSCN$: C, 50.61; H, 3.82; N, 11.81; S, 20.27; SCN^-, 12.3. Found: C, 50.87; H, 4.10; N, 11.42; S, 19.82; SCN^-, 12.9.

This same salt was obtained directly from cephalothin by the following procedure. A solution of 200 g (0.46 mole) of cephalothin, 908 g (9.5 moles) of potassium thiocyanate, 50 ml (0.75 mole) of pyridine, and 10 ml of 85% phosphoric acid in 200 ml of water (pH 6.5) was heated at 60° for 5 hr with stirring.

The reaction mixture was cooled to room temperature and diluted to 4 l. with water. It was extracted with chloroform (five 200-ml portions) and dissolved chloroform was removed under reduced pressure. After cooling to 0°, the aqueous layer was acidified to pH 2.0 by dropwise addition of 6 *N* hydrochloric acid with stirring. Maintaining the mixture at 0° for 3 hr with stirring afforded 163 g (75%) of product.

A portion of this salt from the reaction mixture was converted to cephaloridine in the following manner. A 25-g sample was slurried with 50 ml of water and 150 ml of 25% Amberlite LA-1 (basic form) in MIBK for 30 min. The resulting aqueous solution was extracted with 25% Amberlite LA-1 (acetate form) in MIBK (three 50-ml portions) and with MIBK (50 ml). After stirring at 5° for 1 hr, the betaine, 11.5 g (52%), was collected. This material was identical with that obtained without isolation of the salt.

Cephaloridine Hydriodide.—A solution of 10.0 g (0.024 mole) of cephaloridine and 5.0 g (0.03 mole) of potassium iodide in 200 ml of water was cooled to 5° and 10% hydrochloric acid was added dropwise until no further precipitate formed. The yield of product was 10.0 g (76%); $\lambda_{max}^{H_2O}$ 237 mμ (ε 24,350) and 255 mμ (ε 13,850).

Anal. Calcd for $C_{19}H_{17}N_3O_4S_2 \cdot HI$: C, 41.99; H, 3.34; I, 23.36; N, 7.73; S, 11.80. Found: C, 41.87; H, 3.98; I, 23.63; N, 7.46; S, 11.62.

This hydriodide salt (168 g, 65%) was obtained from 200 g (0.46 mole) of cephalothin, 300 g (1.80 moles) of potassium iodide, 50 ml (0.75 mole) of pyridine, 5 ml of 85% phosphoric acid, and 200 ml of water by reaction and work-up analogous to that of the hydrothiocyanate salt. A sample was converted to cephaloridine in 45% yield *via* the same method used on the hydrothiocyanate salt.

(8) J. L. Spencer, F. Y. Siu, E. H. Flynn, B. G. Jackson, M. V. Sigal, H. M. Higgins, R. R. Chauvette, S. L. Andrews, and D. E. Block, *Antimicrobial Agents Chemotherapy*, in press.

(9) Amberlite LA-1 is a high molecular weight, water-insoluble, liquid secondary amine, commercially available from Rohm and Haas Co. The acetate form used in this investigation was prepared as follows. To 1.0 l. of Amberlite LA-1 and 3.0 l. of methyl isobutyl ketone was added 120 ml of glacial acetic acid and the solution was stirred for 5 min. After stirring with 800 ml of water for 25 min, the organic layer was separated for use.

The Use of Benzene in Separating Aromatic Methoxyl Bands in Nuclear Magnetic Resonance Spectroscopy

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The effect of benzene in causing upfield shifts of various peaks in nmr spectra is well known[1] and has been explained as being due to its disk shape and the diamagnetism of regions above and below the plane of the ring,[2] but comparatively little use appears to have been made of the marked variation in diamagnetic shift experienced by methoxyl groups attached to aromatic rings. The technique appears to be particularly valuable in disentangling magnetically nonequivalent methoxyl peaks from one another. Thus, 1,2,3-trimethoxybenzene (1, Figure 1) is a singlet in deuteriochloroform but in benzene (1B, Figure 1), the 1- and 3-methoxyl groups are shifted upfield much more markedly than the 2-methoxyl,[3] presumably owing to steric inhibition of solvation of the latter.

The same effect is seen in 1-bromo-2,3,4-trimethoxybenzene (2 and 2B, Figure 1)[4] where only the 4-methoxyl is not seriously hindered; therefore, this might be assigned to the band at δ 2.70 (ν 60 Mc). However, this assignment must be treated with caution since the absolute magnitude of the shift is nearly twice that of the former case.

Some form of steric hindrance associated with one of the methoxyl groups is necessary in order for the effect to be seen. For example, the methoxyl peaks of 2,3-dimethoxybenzaldehyde (3 and 3B, Figure 1) separate considerably on solvent change while the unhindered methoxyl groups of the isomeric 3,4-dimethoxybenzaldehyde (4 and 4B, Figure 1) do not.

Examples 5–9 illustrate the same effect. Methyl reserpate in deuteriochloroform (8, Figure 1) shows a coincidence of three methoxyl groups at δ 3.92, two methoxyl groups at δ 3.82, and one methoxyl (presumably the aliphatic methoxyl) at δ 3.50. As expected from 1,2,3-trimethoxybenzene, the central methoxyl of the trimethylgallic acid ring is exposed at δ 3.83 in benzene while the two flanking methoxyl groups add to the A-ring methoxyl, presumably at δ 3.71. The ester and aliphatic methoxyl groups are now exposed at higher fields. Irrespective of the assignments, the

(1) For leading references, see K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, Jr., *J. Am. Chem. Soc.*, **86**, 1718 (1964), footnote 38. See also D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965), regarding benzene shifts in the steroid series.

(2) J. R. Zimmerman and M. R. Foster, *J. Phys. Chem.*, **61**, 282 (1957).

(3) These assignments are made on the basis of symmetry.

(4) Traces of impurities are now visible at δ 2.88 and 3.25.

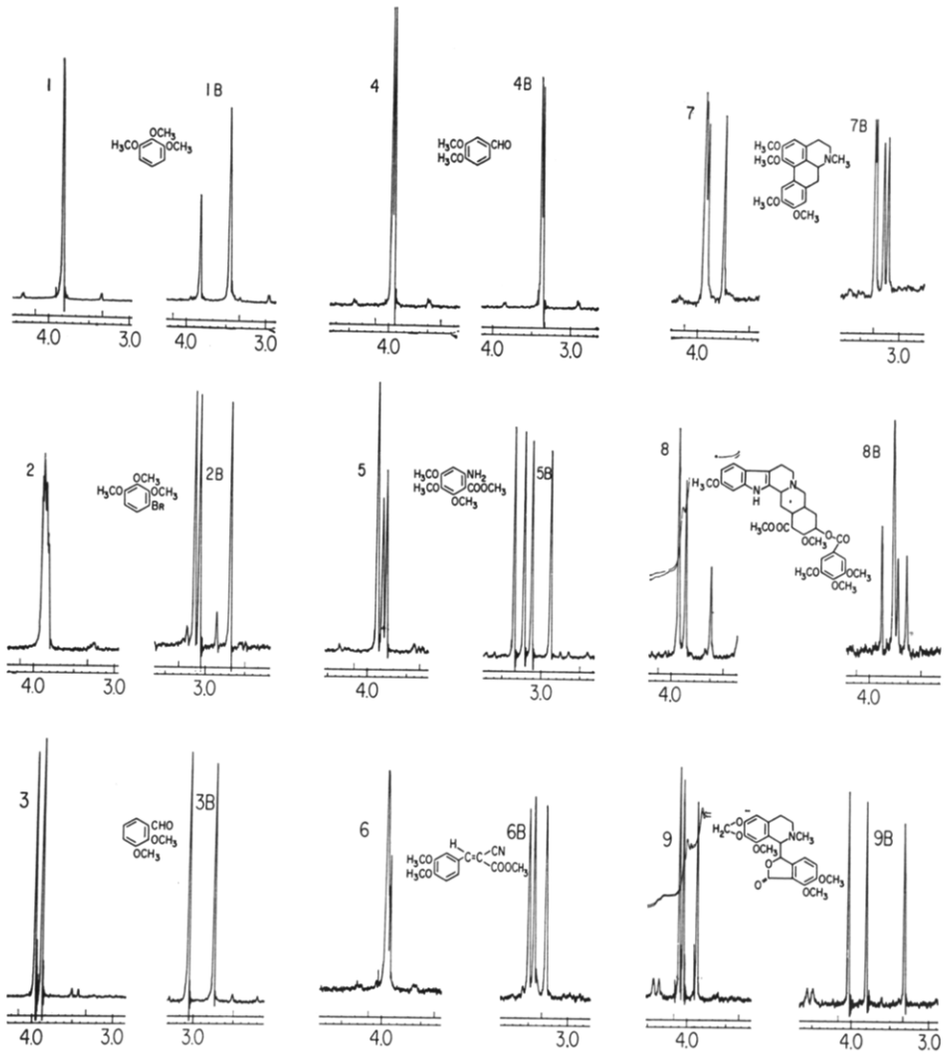

Figure 1.

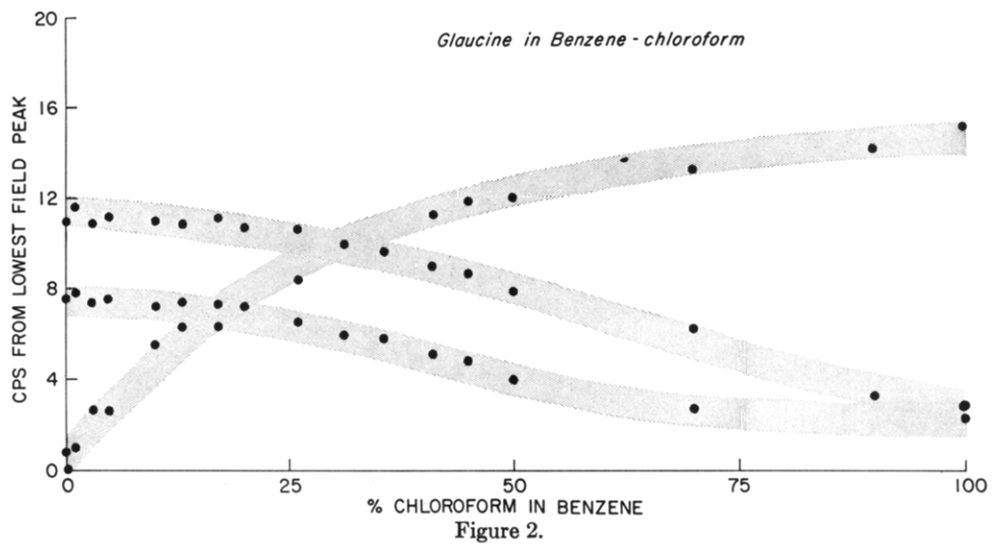

Figure 2.

fact remains that four methoxyl peaks are distinguishable in benzene and only three in deuteriochloroform.

By gradually diluting the sample with benzene the shifts exhibited by the various peaks can be followed. Surprisingly, 3,4-dimethoxybenzaldehyde (4, Figure 1) showed only one peak in a 50% benzene–chloroform mixture suggesting that the methoxyl groups had reversed their relative positions in 100% benzene. This was proved by preparing the 4- and 3-deuteriomethyl derivatives from vanillin and isovanillin, respectively, by the action of deuterated diazomethane.[5] The down-

(5) Merely shaking ethereal diazomethane with an excess of D_2O and a trace of alkali for a few minutes suffices to exchange the protons. The remaining proton on the phenolic group apparently exchanges with the D_2O present in the ether phase *prior* to methylation since only trideuteriomethyl species are found; *cf.* K. J. van der Merive, P. S. Steyn, and S. H. Eggers, *Tetrahedron Letters*, **52**, 3923 (1964), as well as T. D. Goldfarb and G. C. Pimentel, *J. Am. Chem. Soc.*, **82**, 1865 (1960).

field methoxyl is the 4-methoxy group in deuteriochloroform as expected from a simple inductive effect unperturbed by solvation.

In the case of glaucine, shifts caused by dilution were plotted relative to the peak at lowest field (Figure 2). It is again observed that the peak at highest field in 100% chloroform (δ 3.68) is the one which has moved least on dilution with benzene and is therefore nearly superimposed with the lowest field peak (δ 3.34) in pure benzene. It seems very likely that this peak is properly assigned to the 5-methoxyl adjacent to the biphenyl linkage as Goodwin, Shoolery, and Johnson[6] had earlier proposed on the basis of its chemical shift in chloroform alone.

(6) S. Goodwin, J. N. Shoolery, and L. F. Johnson, *Proc. Chem. Soc.*, 306 (1958).

Synthesis of Octamethyloxamidinium Dinitrite and Dinitrate

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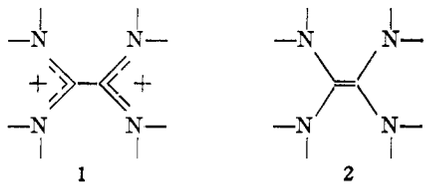
Dinitrate salts of the oxamidinium dication (**1**) derived from tetraaminoethylenes (**2**) have been prepared by oxidation of **2** with silver nitrate[1] or by meta-



1 **2**

thesis of the diiodide salt of **1** and silver nitrate.[2] Pure dinitrate salts are obtained by a separation of colloidal silver or silver iodide. It is to be noted that an excess of dinitrogen tetroxide reacts with tetrakis(dimethylamino)ethylene in *n*-hexane to precipitate octamethyloxamidinium dinitrate directly. In a similar way equimolar amounts of the reactants form the dinitrite salt. This synthesis for dinitrate or dinitrite salts is believed to be a general reaction for fully substituted tetraaminoethylenes. The reactions of tetrakis(dimethylamino)ethylene with other nitrogen–oxygen compounds are extended to include tetranitromethane, nitryl perchlorate, and nitrosyl tetrafluoroborate.

During an investigation of the reaction of tetranitromethane with tetramethyl-2-tetrazene[3] or related compounds, it was observed that equimolar quantities of tetrakis(dimethylamino)ethylene and tetranitromethane produce both octamethyloxamidinium dinitrite and bis(dinitromethanenitronate).[4] In a manner analogous to the effect of excess dinitrogen tetroxide, excess tetranitromethane results in the formation of the dinitrate salt. No evidence for a mixed nitrite or nitrate–dinitromethanenitronate salt was found. The bis(dinitromethanenitronate) and dinitrite or dinitrate salts may be separated by fractional crystallization. The reaction of tetranitromethane with tetrakis(dimethylamino)ethylene is similar to the reaction of the ethylene with carbon tetrahalides,[5] but in the present case octamethyloxamidinium salts are the end products because of the increased stability of the dinitromethanenitronate ion compared with trihalomethyl carbanions.

Nitryl perchlorate or nitrosyl tetrafluoroborate react with tetrakis(dimethylamino)ethylene to give octamethyloxamidinium dinitrite or dinitrate in conjunction with the diperchlorate or bis(tetrafluoroborate) salt. Since the dinitrite or dinitrate salts are readily soluble in water, this reaction provides a novel preparation of the less soluble diperchlorate and bis(tetrafluoroborate) salts.

Experimental Section[6]

Reaction of Tetrakis(dimethylamino)ethylene with Dinitrogen Tetroxide.—Dry nitrogen was bubbled through *n*-hexane for 1 hr at room temperature. To a portion of this solvent dinitrogen tetroxide was added; the concentration of the oxide was estimated by measuring the absorption of the solution at 343 mμ.[7] A typical preparation of dinitrite salt follows. To 0.46 g of tetrakis(dimethylamino)ethylene dissolved in 15 ml of *n*-hexane and placed in a flask purged with dry nitrogen, 0.20 g of dinitrogen tetroxide in *n*-hexane was added. A white solid precipitated immediately which, when dried, gave 0.65 g of a tan solid (98% yield, based on anhydrous dinitrite salt), mp 198°. Recrystallization from ethanol gave a cream-colored solid, mp 209° dec, which exhibited an infrared spectrum identical with that obtained from the reaction of silver nitrite with tetrakis(dimethylamino)ethylene. A spectral maximum corresponding to the octamethyloxamidinium dication was observed at 275 mμ.[8] A colorimetric procedure was used to estimate the amount of nitrite present.[9]

Anal. Calcd for $C_{10}H_{24}N_6O_4 \cdot 0.5H_2O$: C, 39.86; H, 8.36; N, 27.89; NO_2^-, 30.6. Found: C, 40.25; H, 8.21; N, 27.39; NO_2^-, 31.1.

In the preparation of the dinitrate salt a threefold excess of dinitrogen tetroxide was added to the tetrakis(dimethylamino)-ethylene. The precipitate, 3.17 g (96% yield), was washed with ethanol and gave a white solid, mp 266° dec. The ultraviolet spectrum of the material had a maximum at 275 mμ and the infrared spectrum was the same as that of the material produced from the reaction of tetrakis(dimethylamino)ethylene with silver nitrate.

Anal. Calcd for $C_{10}H_{24}N_6O_6$: C, 37.03; H, 7.46; N, 25.91. Found: C, 36.98; H, 7.55; N, 25.72.

Reaction of Tetrakis(dimethylamino)ethylene with Tetranitromethane.—To 1.70 g of tetrakis(dimethylamino)ethylene in *n*-hexane under a protective atmosphere of dry nitrogen, 1.59 g of tetranitromethane in *n*-hexane was added. The resulting solid, 3.28 g (99% yield), was recrystallized from water to give 1.92 g of the bis(dinitromethanenitronate) salt (95% yield), mp 122–124° dec.

Anal. Calcd for $C_{12}H_{24}N_{10}O_{12}$: C, 28.80; H, 4.83; N, 27.99. Found: C, 29.13, 28.85; H, 4.71, 4.86; N, 26.97, 27.10.

An alternative procedure for the separation of the dinitrite or dinitrate salts involved precipitation of these relatively in-

(1) D. M. Lemal, R. A. Lovald, and K. I. Kawano, *J. Am. Chem. Soc.*, **86**, 2518 (1964).

(2) D. M. Lemal and K. I. Kawano, *ibid.*, **84**, 1761 (1962); R. L. Pruett, *et al.*, *ibid.*, **72**, 3646 (1950).

(3) W. E. Thun, D. W. Moore, and W. R. McBride, *J. Org. Chem.*, **31**, 923 (1966).

(4) Since tetramethyl-2-tetrazene is a nitrogen analog of tetrakis(dimethylamino)ethylene [N. Wiberg and J. W. Buchler, *Z. Naturforsch.*, **19b**, 9 (1964)], it was thought that the ethylene analog of 1,1,4-trimethyl-4-(β,β-dinitrovinyl)-2-tetrazene[3] might be formed.

(5) W. Carpenter, *J. Org. Chem.*, **30**, 3082 (1965).

(6) Infrared spectra were obtained from potassium bromide disks (Perkin-Elmer Model 137) and ultraviolet spectra of salts from aqueous solutions (Cary Model 11 MS). Chemical analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn.

(7) C. C. Addison and J. C. Sheldon, *J. Chem. Soc.*, 3142 (1958).

(8) N. Wiberg and J. W. Buchler, *Chem. Ber.*, **96**, 3223 (1963).

(9) B. F. Rider and M. G. Mellon, *Ind. Eng. Chem., Anal. Ed.*, **18**, 96 (1946).