components I, II, III, and resorcinol (IV). As indicated, (1) the protons of aliphatic compounds do experience considerable upfield shifts in the presence of aromatics in aqueous solution; (2) this effect is absent in acetone solution; (3) there is a qualitative correspondence between the nonpolar character of the aliphatics and the magnitude of the anomalous shifts; (4) resorcinol (IV), which is more polar (*i.e.*, interacts more favorably with the solvent water) and has a smaller diamagnetic anisotropy than I, is much less effective than I in causing the anomalous shift; and (5) the two different types of protons of a given aliphatic component (*e.g.*, neopentyl or ethyl alcohol)[6] are shifted to about the same extent, probably indicating the nonspecific nature of the hydrophobic bonding between the aromatic and aliphatic moieties.

Dilution of the aqueous solutions leads to less shielding,[7] and when the concentration of the aliphatic component is increased at constant aromatic concentration slight downfield shifts are observed for both the aliphatic and aromatic protons. All of these observations are consistent with the formation of aggregates.

A further indication of the considerable effect of hydrophobic bonding is the 13-fold increase in solubility of neopentyl alcohol in a 2.5 *m* solution of III as compared to pure water.

Finally, it may be noted that one of the aliphatic substances, DSS (the sodium salt of 4,4-dimethyl-4-silapentane-1-sulfonic acid) has been recommended[8] as an internal standard for aqueous solutions. Since the peak due to the methyl protons of DSS does exhibit a particularly large shift upon addition of the aromatics, clearly there are circumstances in which the use of this salt as an internal standard should be avoided and in which water itself could serve the purpose more satisfactorily.

(6) This is also true for propionic acid and for the α- and ω-protons of 1-butanol.

(7) A plot of the chemical shift *vs.* concentration of the organic component gives a curve, the initial steep slope of which levels off at higher concentrations. A series of these curves will be presented and discussed in the complete paper.

(8) G. V. D. Tiers, Abstracts, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 1960, p. 17R.

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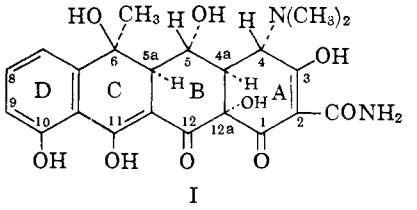
The Stereochemistry at C-5 in Oxytetracycline

Sir:

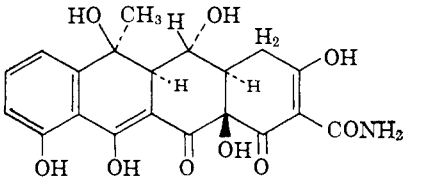
While the structure of oxytetracycline (I) has been known for many years,[1] its configuration has been the subject of several investigations. The early[1] assignments at C-4a, C-5a, C-6, and C-12a have been confirmed subsequently by X-ray data[2,3] which also showed conclusively that the stereochemistry at C-4 differed from that suggested originally. The configuration at



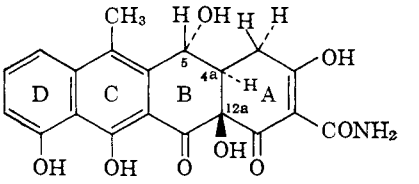
I

C-5, however, has not yet been determined unequivocally, since interpretations of the X-ray data led to conflicting conclusions. We wish to present evidence obtained by n.m.r. spectroscopy that the configuration of oxytetracycline is as shown by structure I. The hydroxyl group at C-5 is *trans* to that at C-6.

For the purpose of a configurational assignment at C-5 by means of n.m.r. spectroscopy oxytetracycline (I) and most of its derivatives are not suitable, since they may assume a variety of conformations. 12a-*epi*-Dedimethylaminoanhydrooxytetracycline (III), however, can exist in one conformation only, determined by the *trans* junction of the A–B rings. In this molecule the proton at C-5 has to be either in a *trans* diaxial or in an equatorial–axial relationship to the proton at C-4a, depending upon the configuration at C-5. The conclusive stereochemical assignment became possible when the n.m.r. spectrum (pyridine) of III showed the signal for the C-5 proton to be a doublet (5.7 p.p.m. from TMS) with an apparent coupling constant of $J = 8$ c.p.s. The protons at C-5 and C-4a thus are *trans* diaxial and the hydroxyl group at C-5 is *cis* to the hydrogen atom at C-4a.



II



III

trans-Junction of the A–B rings in the oxytetracycline skeleton was achieved in the following manner. Treatment of dedimethylamino-12a-deoxyoxytetracycline[1] with *m*-chloroperbenzoic acid in chloroform yielded (75%) dedimethylamino-12a-*epi*-oxytetracycline (II) in its C-11,C-12 diketonic tautomeric form. *Anal.* Calcd. for $C_{20}H_{19}O_9N$: C, 57.55; H, 4.59; N, 3.36. Found: C, 57.12; H, 4.68; N, 3.51. Spectral data showed: λ_{max} (KBr or dioxane) 5.8 μ; $\lambda_{max}^{MeOH-0.01NHCl}$ 262 and 335 mμ (log ϵ 4.37 and 3.67); $\lambda_{max}^{MeOH-0.01NNaOH}$ 249, 260, and 379 mμ (log ϵ 4.21, 4.23, and 4.16). Reacidification of a basic solution showed $\lambda_{max}^{MeOH-HCl}$ 262 and 357 mμ (log ϵ 4.22 and 4.20).

Treatment of II with refluxing 0.8 *N* hydrochloric acid in aqueous acetone yields III (95%). *Anal.* Calcd. for $C_{20}H_{17}O_8N$: C, 60.16; H, 4.29; N, 3.51. Found: C, 59.73; H, 4.64; N, 3.48. Spectral data showed $\lambda_{max}^{MeOH-0.01NHCl}$ 224, 268, and 413 mμ (log ϵ

(1) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings, and R. B. Woodward, *J. Am. Chem. Soc.*, 75, 5455 (1953).

(2) (a) S. Hirokawa, Y. Okaya, F. M. Lovell, and R. Pepinsky, *Acta Cryst.*, 12, 811 (1959); (b) *Z. Krist.*, **112**, 439 (1959); (c) Y. Takeuchi and M. T. Buerger, *Proc. Natl. Acad. Sci. U. S.*, **46**, 1366 (1960).

(3) J. Donohue, J. D. Dunitz, K. N. Trueblood, and M. S. Webster, *J. Am. Chem. Soc.*, **85**, 851 (1963).

4.49, 4.63, and 3.92); $\lambda_{max}^{MeOH-0.01NNaOH}$ 232, 266, 340, and 418 mμ (log ε 4.45, 4.53, 3.77, and 4.08).

Unusual features of the tautomerism of II and the stability of III have been discussed previously.[4]

(4) L. H. Conover, Special Publication No. 5, The Chemical Society, London, 1956, p. 48.

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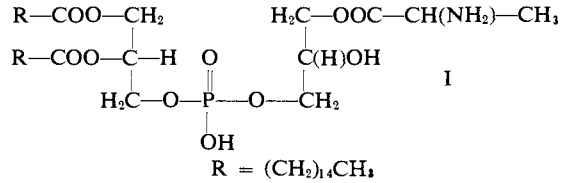
Synthesis of Amino Acid-Esters of Phosphatidylglycerols

Sir:

Various investigators have reported the formation of lipoamino acid complexes in tissue preparations and in microorganisms.[1-7] Apart from the fact that these complexes were usually found in the phospholipid fractions, little was known regarding their chemical structure. Recently, MacFarlane reported[8] that the phospholipid fraction in a batch of *Clostridium welchii* was bound almost entirely to amino acids, and she presented experimental evidence which suggests strongly that the lipoamino acid complexes are amino acid esters of phosphatidylglycerol. The phosphatidyl moiety of the lipoamino acid complexes is presumed to have the same structure and configuration as in phosphatidylglycerol. The amino acids, which were found to consist of alanine, glutamic acid, aspartic acid, lysine, and possibly arginine and histidine, were arbitrarily assigned the terminal position in the fatty-acid-free glycerol moiety. Further evidence, supporting the structure proposed by MacFarlane, was reported by Sinha, Fogel, and Gaby[9] and Vorbeck and Marinetti.[10] However, without definite knowledge of the position of the amino acids in these complexes proof of the structure cannot be considered complete. For this reason, we have synthesized an alanine ester of α-(L-α-phosphatidyl)glycerol having the structure proposed by MacFarlane for the lipoamino acid complexes.[8] In it the amino acid is attached to the terminal hydroxyl of the fatty-acid-free glycerol moiety (formula I). The compound was obtained *via* the following



I

(1) R. W. Hendler, *Science*, **128**, 143 (1958).
(2) R. W. Hendler, *J. Biol. Chem.*, **234**, 1473 (1959).
(3) W. L. Gaby, R. N. Naughten, and C. Logan, *Arch. Biochem. Biophys.*, **82**, 38 (1959).
(4) W. L. Gaby, H. L. Wolin, and I. Zajac, *Cancer Res.*, 20, 1508 (1960).
(5) W. L. Gaby and R. Silberman, *Arch. Biochem. Biophys.*, **87**, 188 (1960).
(6) G. D. Hunter and R. A. Goodsall, *Biochem. J.*, **74**, 34P (1960).
(7) G. D. Hunter and R. A. Goodsall, *ibid.*, **78**, 564 (1961).
(8) M. G. MacFarlane, *Nature*, **196**, 136 (1962).
(9) D. B. Sinha, S. Fogel, and W. L. Gaby, *Federation Proc.*, **23**, 221 (1964).
(10) M. L. Vorbeck and G. V. Marinetti, *ibid.*, **23**, 375 (1964).

series of intermediates: α,γ-benzylideneglycerol → α,γ-benzylidene-β-benzylglycerol → β-benzylglycerol → α-azidopropionyl-β-benzylglycerol [$n^{26}D$ 1.5147, d^{25}_4 1.180. *Anal.* Calcd. for $C_{13}H_{17}O_4N_3$: C, 55.90; H, 6.13; N (Kjeldahl), 5.02; N (Dumas), 15.04. Found: C, 56.10; H, 6.06; N (Kjeldahl), 4.60; N (Dumas), 14.05] → α-(dipalmitoyl-L-α-glycerylphosphoryl)-β-benzyl-α′-(2-azidopropionyl)glycerol [m.p. 27.5–28.5°, $[\alpha]^{23}D$ +2.9° (c 10, chloroform). *Anal.* Calcd. for $C_{54}H_{88}O_{11}N_3P$: C, 65.76; H, 8.99, P, 3.14, N (Kjeldahl), 1.42; N (Dumas), 4.26. Found: C, 65.41; H, 8.81; P, 3.06; N (Kjeldahl), 1.37; N (Dumas), 4.63] → α-(dipalmitoyl-L-α-glycerylphosphoryl)-α′-(2-aminopropionyl)glycerol [m.p. 164–165°, meniscus formation, $[\alpha]^{23}D$ +6.6° (*c* 10, chloroform). *Anal.* Calcd. for $C_{41}H_{80}O_{11}NP$: C, 62.01; H, 10.16; N (Kjeldahl), 1.76; N (Dumas), 1.76; P, 3.90. Found: C, 62.16; H, 9.98; N (Kjeldahl), 1.73; N (Dumas), 1.86; P, 3.81].

The synthesis of the corresponding glycine ester of L-α-phosphatidyl-α-glycerol is in progress in this laboratory.

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Conjecture on the Composition of Dilute Alkali Metal–Ammonia Solutions

Sir:

There is evidence from calculated values of the electron affinities of the alkali metals[1] that their anions should be stable in the gas phase. This stability should be enhanced in polar solvents as the result of ionic solvation.[2] For this reason, we conjecture that such solvated anionic species are constituents of solutions of the alkali metals in liquid ammonia. We propose that these species are involved in an oxidation–reduction equilibrium (eq. 1) involving solvated metal

$$M^+ + 2S^- \rightleftharpoons M^- + 2S \qquad (1)$$

cations and solvent where all species are assumed to be solvated, M^+ is the metal cation, S is the solvent, M^- is the metal anion, and S^- is a solvent anion, *i.e.*, solvated electron. In addition, we propose that ion pairing occurs according to

$$M^+ + A^- \rightleftharpoons M^- \cdot A^- \qquad (2)$$

where A^- is either S^- or M^-. For dilute solutions, to which we restrict ourselves, the presence of higher ionic multiples may be disregarded.[3]

By assuming that ion pairing is nonspecific, that the related equilibrium constant K_2 is given by Fuoss'

(1) E. Clementi, *Phys. Rev.*, 133, A1274 (1964).
(2) R. M. Noyes, *J. Am. Chem. Soc.*, **84**, 513 (1962).
(3) Estimates of ion triples by the Bjerrum-Kraus-Fuoss theory (R. M. Fuoss and C. A. Kraus, *ibid.*, **55**, 2387 (1933)) would indicate that these species are relatively unimportant for concentrations of total metal less than *ca.* 0.1 *M*.