

incubations. Financial support was provided in part by a grant-in-aid from the American Heart Association (R. B. C.) and in part by research grants from the National Institutes of Health and the National Science Foundation (E. E. v. T.).

(16) National Institutes of Health Postdoctoral Fellow.

E. E. van Tamelen, J. D. Willett<sup>16</sup>  
Department of Chemistry

R. B. Clayton, Kathryn E. Lord  
Department of Psychiatry  
Stanford University, Stanford, California  
Received September 29, 1966

### Magnetic Resonance Studies of Ion Solvation. The Coordination Number of Gallium(III) Ions in Aqueous Solutions

Sir:

An extensive  $^{17}\text{O}$  nuclear magnetic resonance study of aqueous solutions containing  $\text{Ga}^{3+}$  ions has been carried out. Herein are reported the results of the coordination number determinations.<sup>1</sup>

Two independent methods were used to determine the number of water molecules in the sphere of hydration of the  $\text{Ga}^{3+}$  ions. The coordination number was determined from the ratio of areas of the bound to the free water, where one is shifted relative to the other by the addition of  $\text{Co}^{2+}$  ions, and also was determined from a measurement of the shift of the free water relative to reference pure water.<sup>2-4</sup>

To pure water containing about 10%  $^{17}\text{O}$  and acidified with perchloric acid four successive amounts of cobaltous perchlorate were added. The paramagnetic shift of the  $^{17}\text{O}$  of the water molecules was measured relative to a pure water reference. The following results obtained are given in Table I. Extrapolation of these results to 1 mole of  $\text{Co}^{2+}$ /55.5 moles of  $\text{H}_2\text{O}$  gives 11000 cps, corresponding to 1905 ppm.

Table I<sup>a</sup>

Detmn	$n_{\text{H}_2\text{O}}$	$n_{\text{HClO}_4}$	$n_{\text{Co}(\text{ClO}_4)_2}$	$\Delta f_{\text{ref/sol}}$ , cps
1	59.64	0.95	0.0598	600
2	60.13	0.95	0.1303	1320
3	60.59	0.95	0.1973	1972
4	60.96	0.95	0.2498	2615

<sup>a</sup> Amounts expressed in millimoles; the four points were on a straight line.

To solution 4, 0.5805 g of  $\text{Ga}(\text{ClO}_4)_3 \cdot (9.38 \pm 0.23) \cdot \text{H}_2\text{O}$  was added. The measured paramagnetic shift for this solution was 2370 cps, whereas the calculated is 2142 cps. Assuming that the increase in the observed shift relative to the calculated is caused by the  $\text{Ga}^{3+}$  ions retaining part of the water in the hydration sphere, the coordination number is calculated to be  $6.28 \pm 0.26$ .

For the same solution the ratio of the areas of the absorption signals of the bound to the free water

yielded a coordination number of  $5.89 \pm 0.20$  (as an average of four signals).

The two methods are seen to be in good agreement. They are, however, sensitive to different factors. The method, based on the measurement of the shift itself, requires accurate determination of the water of hydration of the salt. As a matter of fact the error in the coordination number of the ion in the solution will be the error in the determination of the hydration of the salt. On the other hand, the method based on the ratio of the areas of the free to the bound water signals will not require this. The advantage of the method based on the measurement of the shift is that it is easier to measure the shift of the water in bulk than to measure areas. In particular the measurement of the area of the bound water to the desired precision—accurately enough to determine the hydration numbers—is very elaborate. Depending on the circumstances one of the two methods should be preferred. In the case of the  $\text{Ga}^{3+}$  ion the experimental error of the two methods came out to be about the same.

As given above, the paramagnetic shift of the free water relative to the pure water was found to be 2370 cps. The shift of the free water relative to the bound was  $2190 \pm 10$  cps. Hence there is a paramagnetic shift of 180 cps of the bound water relative to the pure.

The width of the bound water signal at  $35^\circ$  was 753 cps. The width of the free water signal was 580 cps.

(5) Work performed at the Lawrence Radiation Laboratory, University of California, Berkeley, Calif.

Daniel Fiat<sup>5</sup>

Isotope Department, The Weizmann Institute of Science  
Rehovoth, Israel

Robert E. Connick

Department of Chemistry, University of California  
Berkeley, California

Received August 26, 1966

### Complete Sequence of Biosynthesis from *p*-Hydroxybenzoic Acid to Ubiquinone<sup>1</sup>

Sir:

A complete biosynthetic sequence can now be formulated for the pathway from *p*-hydroxybenzoic acid (I) to ubiquinone (IX). Since *p*-hydroxybenzoic acid is a precursor for ubiquinone in various microorganisms<sup>2</sup> and in animals,<sup>2-4</sup> this sequence may be generic for many species of life utilizing ubiquinone in electron transfer of respiration and coupled phosphorylation. However, the diversity of life utilizing ubiquinone may signify that pathways alternative to this sequence will be found.

Four new quinones, apparent precursors of ubiquinone, have been isolated by extensive fractionation of a lipid extract from *Rhodospirillum rubrum*. Structural studies show these products to be 2-decaprenyl-6-methoxy-3-methyl-1,4-benzoquinone (VII,  $n = 10$ ),

(1) Coenzyme Q. LXXXI.

(2) W. W. Parson and H. Rudney, *Proc. Natl. Acad. Sci. U. S.*, **51**, 444 (1964).

(3) R. E. Olson, R. Bentley, A. S. Aiyar, G. H. Dialameh, P. H. Gold, V. G. Ramsey, and C. M. Springer, *J. Biol. Chem.*, **238**, PC3146 (1963).

(4) A. S. Aiyar and R. E. Olson, *Federation Proc.*, **23**, 425 (1964).

(1) The results of the kinetic study will be published elsewhere.

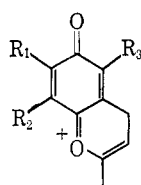
(2) A. Jackson, J. Lemons, and H. Taube, *J. Chem. Phys.*, **33**, 553 (1960).

(3) R. E. Connick and D. N. Fiat, *ibid.*, **38**, 1349 (1963).

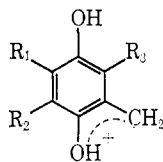
(4) M. Alei and J. A. Jackson, *ibid.*, **41**, 3402 (1964).



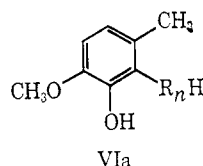
spectrometric analysis. Specifically, peaks with appropriate relative intensities were observed at  $m/e$  818 (M), 803 (M - 15), 191 (Xc), and 153 (XIc). Although isolation of a pure sample of this compound has not yet been achieved, these data support its presence. The possibility that the conversion V  $\rightarrow$  VII could occur *via* 2-decaprenyl-6-methoxy-3-methylphenol (VIa) led to a search for this phenol derivative which has not yet been successful, but is continuing.



Xa,  $m/e$  235,  $R_1=R_2=\text{OCH}_3$ ;  $R_3=\text{CH}_3$   
b,  $m/e$  205,  $R_1=\text{H}$ ;  $R_2=\text{OCH}_3$ ;  $R_3=\text{CH}_3$   
c,  $m/e$  191,  $R_1=R_3=\text{H}$ ;  $R_2=\text{OCH}_3$



XIa,  $m/e$  197  
b,  $m/e$  167  
c,  $m/e$  153



VIa

**Acknowledgment.** We are grateful to Dr. Raffaele F. Muraca and Mrs. Julia S. Whittick for the mass spectra which have significantly aided structural elucidation. This research was partially supported by the Merck Sharp and Dohme Research Laboratories, Rahway, N. J., and we express our appreciation to Dr. Max Tishler.

(17) On leave of absence from The Royal Veterinary and Agricultural College, Copenhagen, Denmark.

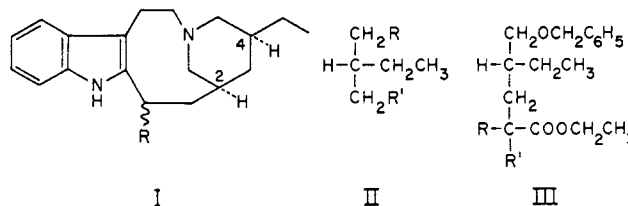
Palle Friis,<sup>17</sup> G. Doyle Daves, Jr., Karl Folkers  
Stanford Research Institute  
Menlo Park, California  
Received August 22, 1966

### The Total Synthesis of *dl*-Dihydrocleavamine, *dl*-Carbomethoxydihydrocleavamine, *dl*-Coronaridine, and *dl*-Dihydrocatharanthine. A General Entry into the Iboga and Vinca Alkaloids

Sir:

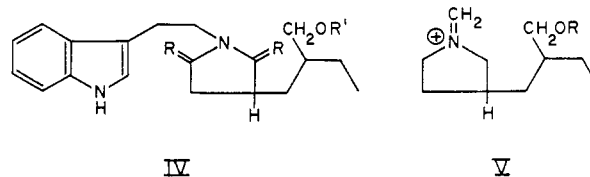
Previous communications from our laboratory<sup>1-3</sup> have demonstrated the utility of a transannular cyclization approach in the synthesis of Aspidosperma, Vinca, and Iboga alkaloids. The stereochemical problems associated with the total syntheses of such molecules are simplified considerably by this method, since we have shown<sup>4,5</sup> that stereospecificity can be achieved and, therefore, the crucial nine-membered ring intermediates are amenable to laboratory synthesis without serious consideration of stereochemistry at the various stages of the synthetic pathway. Very

recently<sup>6</sup> we described a new total synthesis of *dl*-quebrachamine, the essential intermediate for the Aspidosperma series, and now we report our work on the total synthesis of dihydrocleavamine (I; R = H) and its ester derivative (I; R = COOCH<sub>3</sub>) which are the necessary intermediates for the Iboga and Vinca series.



The monosodium salt of 2-ethyl-1,3-propanediol (II; R = R' = OH) on reaction with benzyl chloride in xylene provided the benzyl ether II (R = OH, R' = OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>)<sup>7</sup> in 77% yield, bp 130–133° (2 mm), which was converted to the chloride II (R = Cl, R' = OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, 66% yield), bp 88–90° (0.3 mm), in a conventional manner (thionyl chloride in dimethylaniline). The latter substance was alkylated onto the sodio derivative of diethyl malonate to obtain the diester III (R = H, R' = COOCH<sub>2</sub>CH<sub>3</sub>, 70% yield), bp 155–160° (0.3 mm). This compound was alkylated (sodium in ether) with ethyl bromoacetate to yield the triester III (R = CH<sub>2</sub>COOCH<sub>2</sub>CH<sub>3</sub>, R' = COOCH<sub>2</sub>CH<sub>3</sub>, 78% yield), bp 195–200° (0.2 mm), which in turn was hydrolyzed (alkali), thermally decarboxylated (170°) to a diacid, and finally esterified (ethanol-sulfuric acid) to provide the desired succinate ester derivative III (R = CH<sub>2</sub>COOCH<sub>2</sub>CH<sub>3</sub>, R' = H, 78% yield).<sup>8</sup>

Condensation of the succinate with tryptamine provided, in 77% yield, the succinimide IV (R = O, R' = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>, which exhibited the following spectral properties:  $\lambda_{\text{max}}^{\text{EtOH}}$  222, 274 (sh), 283, and 291  $\mu$ ;  $\nu_{\text{lim}}$  5.68 and 5.90  $\mu$ ; nmr signals:<sup>9</sup>  $\tau$  3.0 (doublet,  $\alpha$  proton on indole), 5.5 (singlet, C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>O), 6.25 (triplet, CH<sub>2</sub>N), 6.65 (broad doublet, OCH<sub>2</sub>CH<), 6.8–8.0 (5 H, CH<sub>2</sub>CH<sub>2</sub>N, CH<sub>2</sub>CO, and >CHCO), and 9.15 (triplet, CH<sub>3</sub>). Lithium aluminum hydride reduction of the latter provided the amine IV (R = H<sub>2</sub>, R' = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, 90% yield), which still retained the normal indole absorption in the ultraviolet



(6) J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *J. Am. Chem. Soc.*, **88**, 3656 (1966).

(7) Satisfactory elemental analyses were obtained for all new compounds reported. In addition, high-resolution mass spectrometry, using an AEI MS9 mass spectrometer, was employed in most instances to establish the molecular formulas.

(8) It must be emphasized again that no separation of the individual stereoisomers is necessary at this point or at subsequent steps in the synthesis, since the stereochemistry of only *one* center, namely C<sub>2</sub>, in dihydrocleavamine determines the total stereochemistry of the final cyclization product. Since the absolute configuration of 4 $\beta$ -dihydrocleavamine is already established at *both* asymmetric centers,<sup>5</sup> the stereochemistry of the succinate ester and all subsequent synthetic intermediates follows directly. For this reason, no discussion of this problem is presented here, but the problem will be treated in a subsequent detailed paper.

(9) All nmr spectra were measured in deuteriochloroform with tetramethylsilane as the internal standard with a Varian A-60 spectrometer. All signals are reported in  $\tau$  units.

- (1) J. P. Kutney and E. Piers, *J. Am. Chem. Soc.*, **86**, 953 (1964).
- (2) J. P. Kutney, R. T. Brown, and E. Piers, *ibid.*, **86**, 2286 (1964).
- (3) J. P. Kutney, R. T. Brown, and E. Piers, *ibid.*, **86**, 2287 (1964).
- (4) A. Camerman, N. Camerman, J. P. Kutney, E. Piers, and J. Trotter, *Tetrahedron Letters*, 637 (1965).
- (5) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, **44**, 637 (1966).