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.).

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

Sir:

An extensive ^{17}O nuclear magnetic resonance study of aqueous solutions containing Ga^{3+} ions has been carried out. Herein are reported the results of the coordination number determinations.[1]

Two independent methods were used to determine the number of water molecules in the sphere of hydration of the 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 Co^{2+} ions, and also was determined from a measurement of the shift of the free water relative to reference pure water.[2-4]

To pure water containing about 10% ^{17}O and acidified with perchloric acid four successive amounts of cobaltous perchlorate were added. The paramagnetic shift of the ^{17}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 $Co^{2+}/55.5$ moles of H_2O gives 11000 cps, corresponding to 1905 ppm.

Table I[a]

Detmn	n_{H_2O}	n_{HClO_4}	$n_{Co(ClO_4)_2}$	$\Delta f_{ref/sol}$, 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

[a] Amounts expressed in millimoles; the four points were on a straight line.

To solution 4, 0.5805 g of $Ga(ClO_4)_3 \cdot (9.38 \pm 0.23)$-$H_2O$ 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 Ga^{3+} ions retaining part of the water in the hydration sphere, the coordination number is calculated to be 6.28 ± 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 ± 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 hyration 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 Ga^{3+} ion the experimental error of the two methods came out to be about the same.

As given above, the paramangetic 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 ± 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° was 753 cps. The width of the free water signal was 580 cps.

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

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Complete Sequence of Biosynthesis from *p*-Hydroxybenzoic Acid to Ubiquinone[1]

Sir:

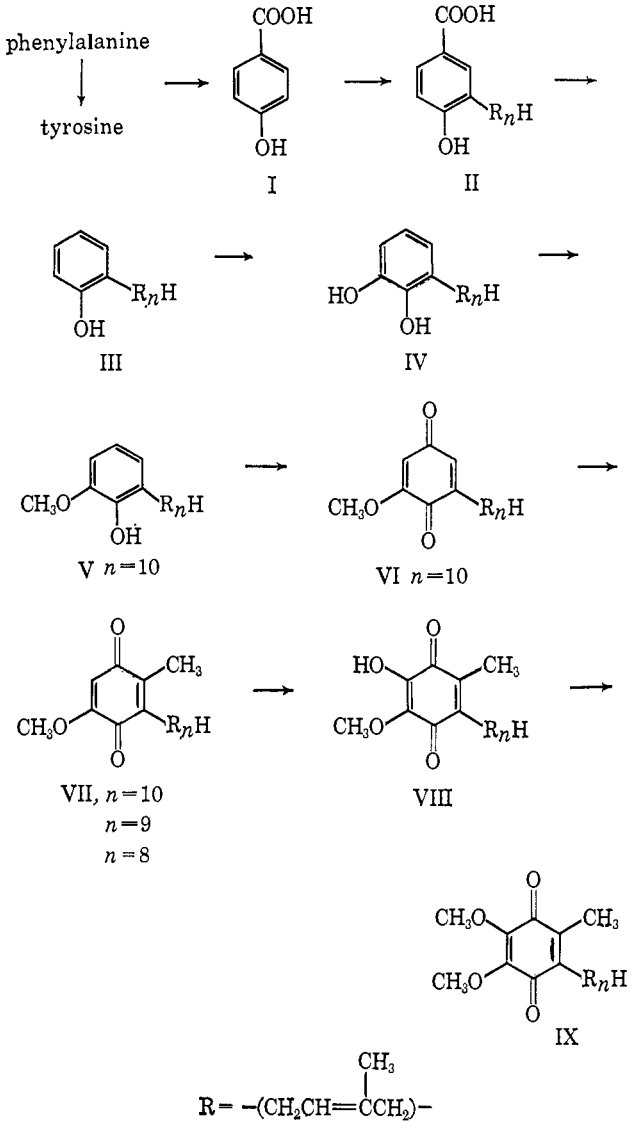
A complete biosynthetic sequence can now be formulated for the pathway from *p*-hydroxybenzoic acid (I) to ubiquinone (IX). Since *p*-hydroxybenzoic acid is a precursor for ubiquinone in various microorganisms[2] and in animals,[2-4] this sequence may be generic for many species of life utilizing ubiquinone 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).

2-nonaprenyl-6-methoxy-3-methyl-1,4-benzoquinone (VII, n = 9), 2-octaprenyl-6-methoxy-3-methyl-1,4-benzoquinone (VII, n = 8), and 2-decaprenyl-6-methoxy-1,4-benzoquinone (VI, n = 10). The compounds VII (n = 10) and VI (n = 10) are apparent precursors of ubiquinone-10. The compounds VII (n = 9) and VII (n = 8) are apparent precursors of ubiquinone-9 and ubiquinone-8, respectively.

Scheme I



The finding of 2-decaprenylphenol (III, n = 10) has been reported from *R. rubrum*[5] and III has been established as a precursor of Q_{10}.[6] Isolation, also from *R. rubrum*, of the structurally related 2-decaprenyl-6-methoxyphenol (V, n = 10),[7] another precursor,[8] led to a partial biosynthetic sequence (I–V).[7]

The isolation of the new 2-decaprenyl-6-methoxy-3-methyl-1,4-benzoquinone (VII, n = 10) and the detection of the new 2-decaprenyl-6-methoxy-1,4-benzoquinone (VI, n = 10) allow this sequence to be completed (Scheme I). The intermediacy of 2-decaprenyl-5-hydroxy-6-methoxy-3-methyl-1,4-benzoquinone (VIII, n = 10) is obvious. This series of transformations is clearly in accord with available knowledge of biological hydroxylations and methylations.[9] The steps of the sequence may now be studied utilizing enzyme preparations.

It is evident that the cells of *R. rubrum* do not produce just a single ubiquinone in a single sequence, but isoprenylation with several pyrophosphates of isoprenoid alcohols occurs to give several ubiquinones. By using the same technique on the ubiquinone fraction from *R. rubrum*, as newly used for the separation of four ubiquinones from *E. coli*,[10] it was possible to show minor amounts of Q_9 and Q_8 besides the major component Q_{10}. The presence of Q_9 as the only ubiquinone in strains of *R. rubrum* has been reported.[11,12]

The lipid extract[13] obtained from *R. rubrum* was fractionated by column chromatography over silica gel by elution with hexane followed by increasing 1% increments of ether in hexane. A fraction eluted with 7% ether in hexane contained an unknown quinone (positive reaction with leucomethylene blue spray reagent). Preparative thin layer chromatography afforded a sample which was shown to be homogeneous by chromatography in a number of systems.

Spectral data (ultraviolet, nmr, and mass spectra) allowed the assignment of this new precursor as 2-decaprenyl-6(5)-methoxy-3-methylbenzoquinone. The mass spectrum shows a molecular ion at m/e 832 and intense peaks at m/e 205 (Xb, base peak) and m/e 167 (XIb). The fragmentation modes giving rise to these two peaks (m/e 205, 167) are known from a study of mass spectra of ubiquinones,[14] where the corresponding fragment ions appear at m/e 235 (Xa, base peak) and 197 (XIa), respectively. The ultraviolet absorption spectrum (λ_{max}^{hexane} 266 and 274 mμ (sh)) is very similar to that of 2,3-dimethyl-5-methoxy-1,4-benzoquinone,[15] nmr spectrum:[16] singlet (free ring H) at τ 4.31; multiplet (vinylic H) at τ 4.98; singlet (methoxyl H) at τ 6.29; doublet (methylene α to the ring) at τ 6.90; alkyl multiplet at τ 8.0–8.44. Ultraviolet and nmr spectra of synthetic models confirmed the structure assignment, but did not distinguish between the 5- and 6-methoxy isomers. That the isolated quinone is 2-decaprenyl-6-methoxy-3-methyl-1,4-benzoquinone (VII, n = 10) is evident from the relationship of this intermediate to compound V.

The mass spectrum of VII also showed peaks at m/e 764 (M), 749 (M − 15) and 696 (M), 681 (M − 15), which indicate the presence of two lower isoprenylogs (VII, n = 9 and 8) as minor components.

The presence in later chromatographic fractions of a second new quinone precursor, 2-decaprenyl-6-methoxy-1,4-benzoquinone (VI, n = 10), was indicated by mass

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(6) W. W. Parson and H. Rudney, *Proc. Natl. Acad. Sci. U. S.*, 53, 599 (1965).
(7) R. K. Olsen, G. D. Daves, Jr., H. W. Moore, K. Folkers, and H. Rudney, *J. Am. Chem. Soc.*, 88, 2346 (1966).
(8) R. K. Olsen, G. D. Daves, Jr., H. W. Moore, K. Folkers, W. W. Parson, and H. Rudney, *ibid.*, in press.
(9) See ref 8 and the references cited therein.
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(12) R. C. Fuller, R. M. Smillie, N. Rigopoulus, and V. Yount, *Arch. Biochem. Biophys.*, 95, 197 (1961).
(13) W. W. Parson and H. Rudney, *J. Biol. Chem.*, 240, 1855 (1965).
(14) R. F. Muraca, *et al.*, unpublished data.
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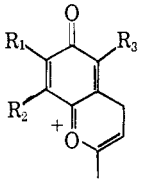
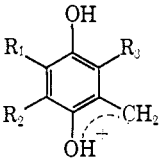
(16) Nmr spectra were taken in CCl_4 solution with a Varian Associates HA-100 with the aid of a time-averaging computer (Varian C-1024 CAT).

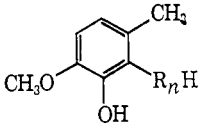
spectrometric analysis. Specifically, peaks with appropriate relative intensities were observed at *m/e* 818 (M), 803 (M − 15), 191 (Xc), and 153 (XIc). Although isolation of a pure sample of this compound has not yet been achieved, these data support its presence. The possibility that the conversion V → 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, $R_1 = R_2 = OCH_3$; $R_3 = CH_3$
b, *m/e* 205, $R_1 = H$; $R_2 = OCH_3$; $R_3 = CH_3$
c, *m/e* 191, $R_1 = R_3 = H$; $R_2 = OCH_3$

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.

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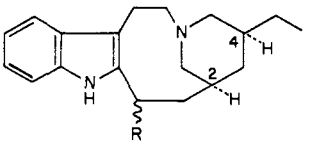
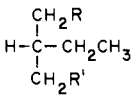
The Total Synthesis of *dl*-Dihydrocleavamine, *dl*-Carbomethoxydihydrocleavamine, *dl*-Coronaridine, and *dl*-Dihydrocatharanthine. A General Entry into the Iboga and Vinca Alkaloids

Sir:

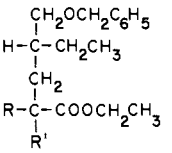
Previous communications from our laboratory[1-3] have demonstrated the utility of a transannular cyclization approach in the synthesis of Aspidosperma, Vinca, and Iboga alkaloids. The stereochemical problems associated with the total syntheses of such molecules are simplified considerably by this method, since we have shown[4,5] 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[6] 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 = $COOCH_3$) which are the necessary intermediates for the Iboga and Vinca series.



I



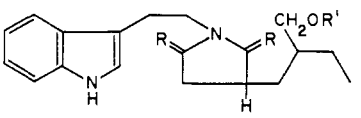
II



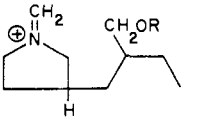
III

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′ = $OCH_2C_6H_5$)[7] in 77% yield, bp 130–133° (2 mm), which was converted to the chloride II (R = Cl, R′ = $OCH_2C_6H_5$, 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′ = $COOCH_2CH_3$, 70% yield), bp 155–160° (0.3 mm). This compound was alkylated (sodium in ether) with ethyl bromoacetate to yield the triester III (R = $CH_2COOCH_2CH_3$, R′ = $COOCH_2CH_3$, 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 = $CH_2COOCH_2CH_3$, R′ = H, 78% yield).[8]

Condensation of the succinate with tryptamine provided, in 77% yield, the succinimide IV (R = O, R′ = $CH_2C_6H_5$), $C_{26}H_{30}N_2O_3$, which exhibited the following spectral properties: λ_{max}^{EtOH} 222, 274 (sh), 283, and 291 mμ; ν_{film} 5.68 and 5.90 μ; nmr signals:[9] τ 3.0 (doublet, α proton on indole), 5.5 (singlet, C_6H_5-CH_2O), 6.25 (triplet, CH_2N), 6.65 (broad doublet, $OCH_2CH<$), 6.8–8.0 (5 H, CH_2CH_2N, CH_2CO, and >CHCO), and 9.15 (triplet, CH_3). Lithium aluminum hydride reduction of the latter provided the amine IV (R = H_2, R′ = $CH_2C_6H_5$, 90% yield), which still retained the normal indole absorption in the ultraviolet



IV



V

(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).
(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_2, in dihydrocleavamine determines the total stereochemistry of the final cyclization product. Since the absolute configuration of 4β-dihydrocleavamine is already established at *both* asymmetric centers,[5] 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 τ units.