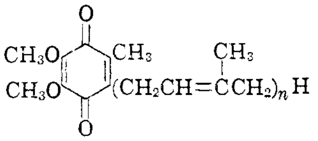
COENZYME Q. II. SYNTHESIS OF 6-FARNESYL- AND 6-PHYTYL-DERIVATIVES OF 2,3-DIMETHOXY-5-METHYLBENZOQUINONE AND RELATED ANALOGS

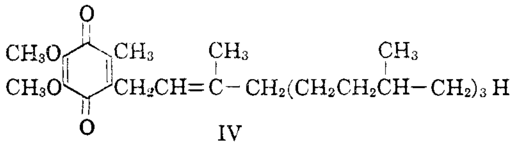
Sir:

Evidence[1,2] was obtained that coenzyme Q is characterized as a group of 2,3-dimethoxy-5-methylbenzoquinones, substituted with homologous isoprenoid chains. A series of such benzoquinones containing isoprenoid substituents in the 6-position was synthesized for comparisons with the coenzyme Q group.

2,3-Dimethoxy-5-methylbenzoquinone[3] was reduced with sulfur dioxide to 2,3-dimethoxy-5-methylhydroquinone, m.p. 77-78°, (*Anal.* Calcd, for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.80; H, 6.71). Reaction of this compound with farnesol and various condensing agents yielded 2,3-dimethoxy-5-methyl-6-farnesylhydroquinone which was oxidized to 2,3-dimethoxy-5-methyl-6-farnesylbenzoquinone, I, red liquid; $\lambda_{\text{max.}}^{\text{isooctane}}$ 272 mμ; ($E_{1\text{ cm}}^{1\%}$, 328); (*Anal.* Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.68; H, 8.87). I also was obtained when the isomeric tertiary alcohol, nerolidol, was substituted for farnesol.



I, $n=3$
II, $n=2$
III, $n=1$



IV

2,3-Dimethoxy-5-methyl-6-geranylbenzoquinone (II)$\lambda_{\text{max.}}^{\text{isooctane}}$ 272 mμ ($E_{1\text{ cm}}^{1\%}$, 440); (*Anal.* Calcd. for $C_{19}H_{26}O_4$: C, 71.67, H, 8.23. Found: C, 72.08; H, 8.00), and 2,3-dimethoxy-5-methyl-6-(3′-methyl-2′-butenyl)-benzoquinone (III)$\lambda_{\text{max}}^{\text{isooctane}}$ 270 mμ ($E_{1\text{ cm}}^{1\%}$, 539); (*Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.26. Found: C, 67.64, H, 7.01) were obtained, respectively, when geraniol and 3-methyl-2-buten-1-ol were substituted for farnesol in the condensation reaction. When phytol was used for the alcohol. 2,3-dimethoxy-5-methyl-6-phytylbenzoquinone (IV) was obtained; $\lambda_{\text{max.}}^{\text{isooctane}}$ 272 mμ ($E_{1\text{ cm}}^{1\%}$,-291) (*Anal.* Calcd for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 76.31; H, 10.60).

Nuclear magnetic resonance spectra of benzoquinones I and II were consistent with the structures assigned and show a broad resonance region,[4] as expected, with center at +8 c.p.s. ($-\text{C}\underline{\text{H}}=$), resonance at −34 c.p.s. ($=\overset{|}{\text{C}}-\text{OC}\underline{\text{H}}_3$), a doublet at −63 and −70 c.p.s. ($=\overset{|}{\text{C}}-\text{C}\underline{\text{H}}_2-\text{CH}=$), resonance at −113 c.p.s. ($=\overset{|}{\text{C}}-\text{C}\underline{\text{H}}_2\text{C}\underline{\text{H}}_2\text{CH}=$ and ring $=\overset{|}{\text{C}}-\text{C}\underline{\text{H}}_3$, which were not resolved in the spectrum at 40 mc.), and resonance at −125 c.p.s. (chain $=\underset{\text{C}\underline{\text{H}}_3}{\underset{|}{\text{C}}}-$). Benzoquinone III showed similar bands with the exception that the band at −113 c.p.s. was due entirely to ring $=\overset{|}{\text{C}}-\text{C}\underline{\text{H}}_3$. The phytyl analog, IV, showed the above bands and an additional doublet at −154 and −159 c.p.s. due to paraffinic protons. The nuclear magnetic resonance spectra for the coenzyme Q group are fully compatible with those of the synthetic compounds.

The infrared spectra in carbon disulfide of compounds I-IV showed bands at 6.03, 6.18 and 7.9 μ characteristic of 2,3-dimethoxybenzoquinone functionality.

Dr. Frederick L. Crane of the Institute for Enzyme Research of the University of Wisconsin and Dr. David Hendlin of our laboratories have found compounds I, II, and IV above active in replacing coenzyme Q_{10} in the isoöctane-extracted ETP succinoxidase system.[5] Details on the enzymatic activities of these compounds will be published shortly.

CONTRIBUTION FROM THE
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[1] R. L. Lester, F. L. Crane and Y. Hatefi, THIS JOURNAL, **80**, 7451 (1958).

[2] D. E. Wolf, C. H. Hoffman, N. R. Trenner, B. H. Arison, C. H. Shunk, B. O. Linn, J. F. McPherson and K. Folkers, *ibid.*, **80**, 7452 (1958).

[3] W. K. Anslow, J. N. Ashley and H. Raistrick, *J. Chem. Soc.*, 439 (1938).

[4] The bands refer to 40 mc. spectra in carbon tetrachloride, + means at lower fields than water protons while − means at higher fields.

[5] F. L. Crane, Y. Hatefi, R. L. Lester and C. Widmer, *Biochim. Biophys. Acta*, **25**, 220 (1957).

BOOK REVIEWS

Chemistry of the Rare Radioelements. Polonium–Actinium. By K. W. BAGNALL, B.Sc., Ph.D., Atomic Energy Research Establishment, Harwell, Eng. Academic Press Inc., Publishers, 111 Fifth Avenue, New York 3, N. Y. 1957. x + 177 pp. 22 × 14.5 cm. Price, $5.00.

Here is a valuable book on a group of six radioelements, Po, At, Fr, Ra and Ac, atomic numbers 84–89. Few chemists, except those in government institutions, have had the opportunity to investigate the properties of all of these radioelements, especially in weighable amounts. Dr. Bagnall is very well informed, in the chemistry and handling of such elements and has made many important contributions to the chemistry of polonium to which about half the space of the book is devoted. He has written "... with the object of collecting all the published data ... and to give some account of the methods used for the study of their chemistry." While the former aim is somewhat unrealized, the author has, on the whole, accomplished his mission successfully.

The book is essentially a concise and critical survey with an excellent bibliography for each element. It is a compact source of well chosen information on each of the radioelements, with emphasis on techniques of separation and tracer chemistry. The general reader cannot but be impressed with the practical importance of the Periodic Table in the development of separation and purification techniques and its aid in understanding the chemical behavior of each radioelement. Dr. Bagnall constantly stresses the importance of the similarities and differences which exist between each radioelement and its homologs: Po and Te; At and I; Fr and Cs; Rn and the inert gases; Ra and Ba; Ac and the rare earths, especially La.

A strong point of the book is the considerable emphasis on the techniques of handling curie-level activities of radioelements. His discussion of health hazards, glove-box techniques, and methods for contamination control is not included as an afterthought, but is the subject of two chapters and is also woven into the text. The reader, therefore, is kept aware of the prime importance of good hot-laboratory techniques. This is no business for careless amateurs, especially when dealing with milligram amounts of elements such as Po^{210} and Ac ^{227}!

ARGONNE NATIONAL LABORATORY
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Gmelins Handbuch der Anorganischen Chemie. Achte Völlig Neu Bearbeitete Auflage. Calcium. Teil B—Lieferung 2. Verbindungen Bis Dithionit. System-Nummer 28. E. H. ERICH PIETSCH, Editor. Verlag Chemie, G.m.b.H., (17a) Weinheim/Bergstr., Germany. 1957. xvi + 392 pp. 17.5 × 25.5 cm. Price, DM 219. ($52.56).

Gmelins Handbuch der Anorganischen Chemie. Achte Völlig Neu Bearbeitete Auflage. Kupfer. Teil B—Lieferung 1. Verbindungen Bis Kupfertellurate. System-Nummer 60. E. H. ERICH PIETSCH, Editor. Verlag Chemie, G.m.b.H., (17a) Weinheim/Bergstr., Germany. 1958. xxvii + 624 pp. 17.5 × 25.5 cm. Price, DM 349.—($83.76).

Gmelins Handbuch der Anorganischen Chemie. 8th Edition. **Systematik der Sachverhalte.** E. H. ERICH PIETSCH, Editor. Verlag Chemie, G.m.b.H., (17a) Weinheim/Bergstr., Germany. 1957. xiv + 116 pp. 17.5 × 25.5 cm. Price, DM 72.—($17.28).

The calcium volume numbered B-2 is actually the first section on the physical and chemical properties of the compounds of calcium, the "B-1" part having covered the technology of both the element and its compounds, material usually given in the "A" volumes of the Gmelin series. The new volume covers the compounds of calcium with the first eight (helium–iodine) of the elements according to the Gmelin system numbers, and some of its compounds with sulfur, no. 9. The volume on copper (B-1) corresponds to "B-2" for calcium, taking up not the technology but the usual physical properties and chemical relations of the compounds; it covers the copper compound with the elements through tellurium (system number 11).

The presentation is all that we have come to expect in these magnificent digests, distinguished by regularity of order, clarity of headings, completeness of information with numerous diagrams and numerical tables, critical evaluation and comments, and full and valuable documentation.

The extreme condensation of the presentation necessitates so many word abbreviations that some of the sentences appear cryptic. At the same time the Handbuch continues to present literature references in its familiar clear and convenient fashion, repeating them fully in every new paragraph or section when necessary. Although some space might be saved by the invention of still another "number system" for this purpose, the clarity and the immediate availability of the references justify the space used.

Both volumes presumably cover the literature through 1949 completely, and the copper volume, it is stated, also includes the literature through 1954 "in special cases." Actually, a considerable number of references through 1953 also appear in the calcium volume. In neither case, however, would the reader be safe in assuming a coverage later than 1949 for any particular item.

The high price for the regular volumes of this series is evidently a necessity, in view of the amount of work obviously going into them. On the other hand the price of the "Systematik," a special volume outside the regular series, is puzzling. Hardly more than a pamphlet, this is a detailed outline covering the headings systematically used in the Handbuch, and it is presented in both English and German, side by side on every page. It offers a numerical cataloguing scheme, with about 2000 headings, of particular value in card-filing and in cross-referencing, for the indexing and filing of the information available in the Handbuch. Although simply an outline of headings, the price is the same as that of the regular Gmelin volumes themselves, namely, about 13 cents per page, with many of the pages, moreover, practically blank.

The price of these books has long ago left the individual behind as a purchaser, but one begins to wonder even how many modestly endowed libraries can afford them. Because of their great value, however, one hopes that every research library can have them available.

DEPARTMENT OF CHEMISTRY
NEW YORK UNIVERSITY JOHN E. RICCI
NEW YORK, N. Y.

Organic Syntheses. Volume 37. JAMES CASON, Editor-in-Chief. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, 16, N. Y. 1957. vii + 109 pp. 15 × 23.5 cm. Price, $4.00.

The importance of "Organic Syntheses" preparations to organic chemists all over the world, whether inexperienced or experienced, students or masters of the art, has been so well-recognized that this new volume needs no more introduction than the announcement of its publication and a listing of the preparations included. The fact that the editor of the current volume is Cason guarantees that its users will find the high level of reliability of procedures and degree of usefulness expected on the basis of the preceding volumes.

Not so well-recognized, particularly among younger chemists, is the tremendous amount of time and effort on the part of the volume editor, the other members of the editorial board and collaborators in their laboratories, as well as by the submitters, which is necessary to ensure this degree of excellence and reproducibility of the preparations included. The careful preliminary screening of every preparation submitted, and the repeated checking in the laboratory of one of the associate editors of each considered potentially suitable—an experimental process that takes more than a week in the best cases and has extended over several years in more than a few—has been the key factor which has ensured the high quality and reproducibility, in the opinion of the reviewer.

In the present volume each preparation was chosen for some useful reason. In some cases this is because the product is of more than limited use or the procedure represents a good example of a generally useful reaction; included are: 2-chloro-2-methylcyclohexanone and 2-methyl-2-cyclohexenone, 2-chloronicotinonitrile, diaminouracil hydrochloride, 1-diethylamino-3-butanone, diethyl benzoylmalonate (use of mixed benzoic-carbonic anhydride), *trans*-2-dodecenoic acid, ethyl *t*-butyl malonate, 4-ethyl-2-methyl-2-octenoic acid, ethyl α-nitrobutyrate, glutaric acid and glutarimide, *n*-heptamide, 3-*n*-heptyl-5-cyanocytosine, 4-hydroxy-1-butanesulfonic acid sultone, isophorone oxide, 3-methyloxindole, nicotinamide-1-oxide, norbornylene, pseudopelletierine, stearolic acid and *ar*-tetrahydro-α-naphthol (lithium-ammonia reduction). Two preparations, benzoylacetanilide and oleoyl chloride, illustrate the utility of a convenient laboratory-size continuous reactor. The remaining procedures, which might well be included in the first category by another reviewer, and apparently were chosen for miscellaneous reasons, including novelty, comprise the following: benzofurazan oxide, 3-benzoylpyridine, 3,4-dinitro-3-hexene, 1,4-diphenyl-5-amino-1,2,3-triazole and its rearrangement to 4-phenyl-5-anilino-1,2,3-triazole, ethyl benzoylacetate (use of aqueous sodium hydroxide for the acylation), parabanic acid and trichloromethylphosphonyl dichloride.

Now that "Organic Syntheses" is nearing the end of its fourth decade, and in light of the advances of modern organic chemistry, the questions are heard: Is the present character of "Organic Syntheses" the best for the future?