pattern *via* a symmetrical intermediate produced from precursor feedings might result from a minor or aberrant pathway. For example, from the results of root XIII the maximum activity at C-4′ that could result from a symmetrical intermediate (C-2′, C-5′ = 2.8%; C-3′, C-4′ = 3.1%) is only 29% of the total. At the other extreme, no biosynthesis may occur by such a path. Therefore, the labeling pattern produced from short-term $^{14}CO_2$ exposure must result predominantly from an unsymmetrical intermediate, and the question of pyrrolidine ring biosynthesis must now be considered anew.

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## Long-Range Mercury-199–Proton Spin–Spin Coupling. I. Substituent Effects in Acyclic Systems

*Sir:*

Recent interest in organomercury chemistry and in the use of nuclear spin–spin coupling in conformational analysis prompts us to communicate in preliminary form our observations on $Hg^{199}$–$H^1$ coupling through $4\sigma$ bonds. Although spin–spin coupling of mercury with protons separated by two and three bonds (*gem*- and *vic*-coupling, respectively) has been reported by several workers, no mention seems to have been made of coupling through four bonds[1] except in cases involving a $\pi$ bond (allylic coupling[2]). This in itself seems surprising, since $4\sigma$ coupling is readily observable in the oxymercuration products of many simple, acyclic olefins, and can be as large as 50 c.p.s.

Each of the compounds reported below was prepared from equimolar amounts of olefin and mercuric acetate in methanol, followed by neutralization with sodium carbonate and removal of the solvent *in vacuo*. The $\beta$-methoxyalkylmercuric acetates were converted to the corresponding chlorides, bromides, and iodides by shaking with excess aqueous potassium halide and subsequent recrystallization. The structures of the adducts followed unequivocally from the observed n.m.r. chemical shifts and relative magnitudes of the large *gem*- and *vic*-$Hg^{199}$–$H^1$ coupling constants[3]; methoxymercuration of all unsymmetrical olefins took place cleanly in the Markovnikov sense. In each case, assignment of the observed satellites of the high-field methyl protons arising from $Hg^{199}$ $4\sigma$ coupling was confirmed by integration (17 ± 1% of the total methyl group area) and by conversion to the corresponding iodomercuric derivative, in which the satellites vanished and the relative area of the remaining methyl resonance increased by the expected amount.[4] No coupling through $5\sigma$ bonds could be observed in compound **9**; the *t*-butyl group appeared as a sharp singlet with symmetrical relaxation envelope.

The values of $J_{4\sigma}$ ($Hg^{199}$–$H^1$) for the 2-methyl group in selected compounds are given in Table I.

**Table I.** Coupling Constants, $J_{4\sigma}$ ($Hg^{199}$–$CH_3$), for Methoxymercuration Products $CH_3CR_1(OCH_3)CR_2R_3HgCl$[a]

| Compd. | $R_1$ | $R_2$ | $R_3$ | $J_{4\sigma}$, c.p.s. |
|---|---|---|---|---|
| **1** | H | H | H | 0 |
| **2**[b] | H | H | $CH_3$ | 7 |
| **3**[b] | H | $CH_3$ | H | 0 |
| **4** | $CH_3$ | H | H | 22 |
| **5** | $CH_3$ | $CH_3$ | H | 22 |
| **6** | $CH_3$ | $CH_3$ | $CH_3$ | 0 |
| **7** | $C_2H_5$ | H | H | 20 |
| **8** | *i*-$C_3H_7$ | H | H | 17 |
| **9** | *t*-$C_4H_9$ | H | H | 27 |
| **10** | *p*-$C_6H_4OCH_3$ | H | H | 20 |
| **11** | $CH_2Cl$ | H | H | 30 |
| **12** | $CH_2Br$ | H | H | 33 |
| **13** | $CH_2C_6H_5$ | H | H | 39 |
| **14** | *p*-$CH_2C_6H_4OCH_3$ | H | H | 44 |
| **15** | 2,4,6-$CH_2C_6H_2(CH_3)_3$ | H | H | 48 |

[a] N.m.r. spectra were recorded at 60 Mc. as 25% solutions in carbon tetrachloride with tetramethylsilane and benzene (2%) as internal references. The estimated uncertainty in $J_{4\sigma}$ values is ±3%. [b] Compound **2**, prepared from *trans*-2-butene, should be the *erythro* isomer; compound **3**, from *cis*-2-butene, the *threo* [*cf.* J. Chatt, *Chem. Rev.*, **48**, 7 (1951)].

Correlation of the observed magnitudes of $J_{4\sigma}$ ($Hg^{199}$–$CH_3$) with expected steric effects of substituents reveals that the mechanism of this coupling is indeed complex.[5] It is tempting to speculate on the relative importance of through-space and through-bond interactions[5] and steric and electronic effects on C–Hg and C–C bond hybridizations and angles, and particularly on the effects of delocalization of unshared electrons or C–Hg and C–C bonding pairs into the available mercury orbitals. (Compare, for example, $J_{4\sigma}$ for compounds **8**–**15** with the positive charge-stabilizing abilities of the groups $R_1$.) A detailed discussion is deferred until a forthcoming paper, to include studies in progress on cyclic compounds of more precisely known geometry. However, it can easily be seen by examination of selected pairs of compounds in Table I that steric effects are important (*e.g.*, **2** *vs.* **3**), as well as electronic effects (*e.g.*, **7** *vs.* **12**; **13** *vs.* **14**). It is equally clear that empirical rules for the prediction of proton–proton $4\sigma$ coupling (the "M" arrangement[5]) and long-range proton–fluorine coupling (the "converging vector rule"[5]) fail badly for $Hg^{199}$–$H^1$ $4\sigma$ coupling when bulky substituents are present, though the former meets with some success in compounds

(1) V. G. Klose [*Ann. Physik*, **10**, 392 (1963)] was unable to detect any $Hg^{199}$ satellites about the methyl triplet in di-*n*-propylmercury.

(2) D. May, M. Emerson, and J. P. Oliver, *Inorg. Chem.*, **2**, 1261 (1963).

(3) P. R. Wells and W. Kitching, *Tetrahedron Letters*, 1531 (1963).

(4) M. D. Rausch and J. R. Van Wazer [*Inorg. Chem.*, **3**, 761 (1964)] and others have suggested that the absence of *gem*- and *vic*-$Hg^{199}$–$H^1$ coupling in alkylmercuric iodides is due to rapid chemical exchange. In support of this assumption, we have observed broadened $Hg^{199}$ satellites in $\beta$-methoxyalkylmercuric iodides which possess certain substituents capable of substantially reducing the rate of exchange (*e.g.*, compound **15**). This phenomenon will be discussed in a forthcoming communication.

(5) For a recent discussion of long-range spin–spin coupling mechanisms, see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 5.

**1–8** if it is assumed that –HgX is considerably larger than –H, but smaller than $-CH_3$.[6]

The potential advantages of mercury–proton splitting in the structural determination of olefinic compounds, as well as in conformational analysis, are numerous. Methoxymercuric halide adducts of olefins can be prepared as rapidly and conveniently as the corresponding dibromides, are more stable, and are free from complications due to carbonium ion rearrangements and conjugate addition.[7] They are generally hydrophobic solids which crystallize in analytical purity from ethanol–water mixtures and are abundantly soluble in carbon tetrachloride. The original olefins can be readily regenerated, if necessary.

Work now in progress in this laboratory suggests that the magnitude of mercury–proton $4\sigma$ coupling is highly sensitive to electronic effects of substituents, foreshadowing some utility in theoretical studies as well.

(6) F. R. Jensen and L. H. Gale [*J. Am. Chem. Soc.*, **82**, 145 (1960), and preceding papers] showed that –HgBr exhibits little or no conformational preference as a substituent on the cyclohexane ring, implying that the long (2.33 Å.) C–Hg bond minimizes 1,3-axial,axial repulsions. That mercury behaves as a large atom toward β-substituents in acyclic compounds is evident from the magnetic nonequivalence of the $-CH_2$-HgCl protons in compounds **1**, **7–9**, and **11–15**. (The methylene protons in **10** are apparently accidentally equivalent.) Magnetic nonequivalence is especially easy to establish in these compounds, since *there are two different* $H^1$–$C$–$Hg^{199}$ *coupling constants;* this is apparently the first reported case in which geminal protons couple nonidentically with a nucleus attached to the same saturated carbon atom. The n.m.r. spectra of compounds **13–15** are particularly striking, since both methylene groups appear as widely spaced AB quartets ($J_{AB}$ = 12–15 c.p.s., $\Delta\nu_{AB}$ = 8–38 c.p.s.) with sharply resolved proton–proton $4\sigma$ coupling ($J$ = 1–1.5 c.p.s.) superimposed on the low-field half of each quartet. The stereoelectronic implications of this result will be discussed in a subsequent communication.

(7) T. G. Traylor, *J. Am. Chem. Soc.*, **86**, 244 (1964), and references cited therein. Breakdown of stereospecificity resulting from the duality of mechanisms discussed by Traylor might prove troublesome with certain strained olefins.

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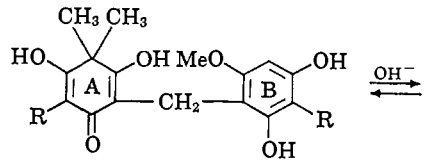
## The Biosynthesis *in Vivo* of Methylenebisphloroglucinol Derivatives

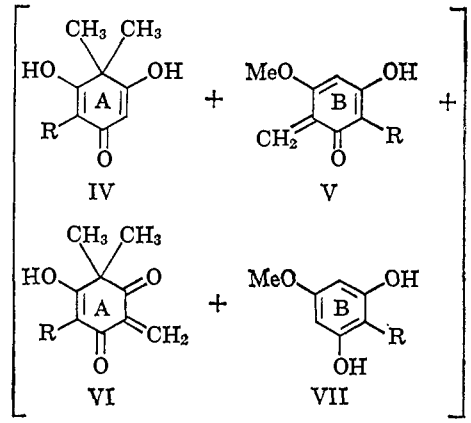
*Sir:*

Dimeric acylphloroglucinol derivatives such as desaspidin (I), margaspidin (II), and albaspidin (III)[1] are presumably derived from acetate and malonate units in the same manner as griseofulvin and quercetin, etc.[2] We have been concerned with later aspects of the biosynthesis, in particular, the source of the methyl and methylene units, the mechanism of the dimerization process, and the sequence in which these events occur.

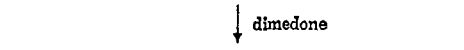
Methionine-methyl-$C^{14}$ (specific activity 11.7 curies/mole, $48.8 \times 10^6$ d.p.m. total) was injected into adult *Dryopteris marginalis* ferns and the aforementioned compounds were isolated (incorporation: 0.76% in raw filicin), purified, and degraded by taking advantage of the "rottlerone change."[3] The methylene carbon



I (0.24 mcurie/mole = 1.00)

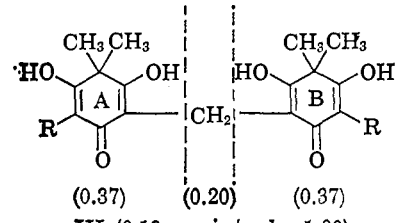


IV V VI VII



dimedone

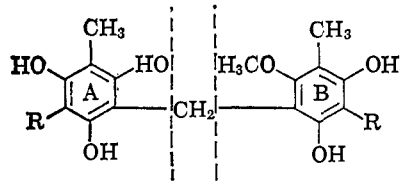
IV (0.50) + VII (0.24) + HCHO dimedone (0.24)



(0.37) (0.20) (0.37)

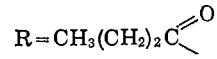
III (0.13 mcurie/mole = 1.00)

+



(0.25) (0.50)

II (0.12 mcurie/mole = 1.00)



was withdrawn from the equilibrium as the dimedone adduct of formaldehyde, and the radioactivity of the liberated monomers (*e.g.*, IV and VII) was used as a measure of the activity of their contained methyl groups.

As expected, the C- and O-methyl groups are derived from methionine (presumably *via* S-adenosylmethionine), and in common with analogous processes[4] all of the methyl carbons are derived with the same efficiency, suggesting that the complete synthesis of a given molecule occurs from one methyl pool.[5]

(1) For the most recent paper in this series see A. Penttila and J. Sundman, *Acta Chem. Scand.*, **18**, 1292 (1964). Margaspidin is a new compound: A. Penttila and G. J. Kapadia, *J. Pharm. Sci.*, in press. This paper was presented in part at the Sixth Annual Meeting of the American Society of Pharmacognosy, June 17, 1965.

(2) For a review see A. J. Birch, *Proc. Chem. Soc.*, 3 (1962).

(3) T. Backhouse, A. McGookin, J. Matchet, A. Robertson, and E. Tittensor, *J. Chem. Soc.*, 113 (1948).

(4) J. F. Snell, A. J. Birch, and P. L. Thomson, *J. Am. Chem. Soc.*, **82**, 2402 (1960).

(5) However, the fact that I has a higher specific activity than either II or III when corrected for the number of methyl and methylene groups present suggests that the sites of their synthesis may differ. In addition, the different activities observed fortuitously remove the objection that equilibration among the various compounds may have occurred in nature or during isolation, *via* the "rottlerone change." Subsequent isolations gave still other ratios of activities between I, II, and III.