This previously unrecognized phenomenon in no way influences our present conclusions and will be discussed in a full paper.

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Synthesis of α-Dehydrobiotin

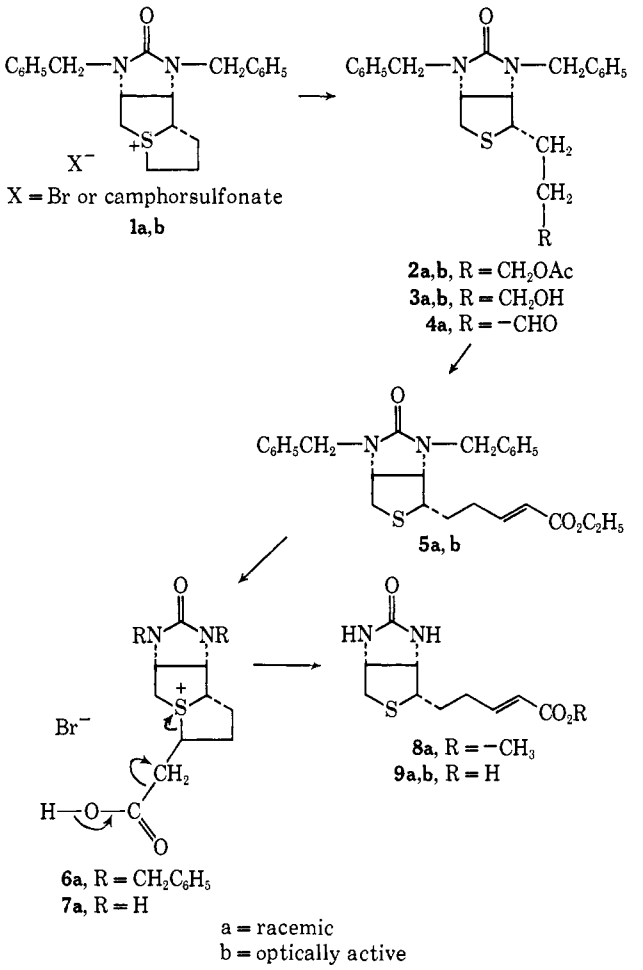
Sir:

The isolation and characterization of *d*-α-dehydrobiotin as a natural antimetabolite of the cofactor biotin with antibiotic properties against a number of microorganisms have been reported.[1] It is the most effective antimetabolite of biotin known, having about five times the potency of *d*-biotin sulfone and 80 times that of *d*-homobiotin in one assay.[1a]

This substance, which may facilitate the study of the biochemistry of biotin, was synthesized as follows. First, as a model, racemic α-dehydrobiotin was prepared by treatment of the racemic sulfonium bromide[2] **1a** with sodium acetate to give the open acetate **2** [mp 100–103°;[3] ir ($CHCl_3$) 1735 (ester C=O) and 1695 cm^{-1} (urea C=O)], which was hydrolyzed with alkali to the alcohol **3a** [mp 105–108°; ir ($CHCl_3$) 3630 (OH) and 1690 cm^{-1} (urea C=O)]. Oxidation of this alcohol to the aldehyde **4a** [mp 110–113°; ir ($CHCl_3$) 1720 (CH=O) and 1690 cm^{-1} (urea C=O); nmr ($CDCl_3$) δ 9.74 ppm (s, 1, $-CHO$)] without concomitant oxidation of the sulfide group was achieved with dicyclohexylcarbodiimide and dimethyl sulfoxide.[4] The additional two carbon atoms were attached by treatment of the aldehyde **4a** with the sodium salt of the triethylphosphonoacetate[5] to give **5a**, mp 96–100°.

Removal of the protecting benzyl groups presented unexpected problems due to the juxtaposition of the double bond and the electron-rich sulfide linkage. Heating of **5a** with 48% hydrobromic acid for 0.5 hr under reflux gave the cyclic sulfonium acid **6a** (mp 214–216°; nmr (DMSO) no band at δ 5–7 ppm); further heating under reflux for 4 hr then gave the debenzylated acid **7a**. Since it was anticipated that treatment of this intermediate with base would cause fragmentation[6] as shown by the arrows, the carboxyl group was esterified by treatment with methanol and hydrogen bromide, and then treated with sodium bicarbonate to give the methyl ester **8a**, mp 169.5–172°, which on alkaline hydrolysis gave *d,l*-α-dehydrobiotin (**9a**), mp 238–240°.

Repetition of this sequence of reactions starting from the *l*-thiophanium *d*-camphorsulfonate (**1b**) with characterization of the following optically active intermediates [**2b**, mp 98–100°, $[\alpha]^{25}D$ −50.3° (*c* 1, $CHCl_3$); **3b**, mp 85–87°, $[\alpha]^{25}D$ −54° (*c* 1, $CHCl_3$); and **5b**, mp 90–92°, nmr (DMSO) δ 5.78 (d, 1, *J* = 16 Hz, $=CH-CO_2Et$), 6.89 ppm (m, 1, $-CH=CH-CO_2Et$)] led to *d*-α-dehydrobiotin (**9b**), mp 256–257.5°, undepressed on addition of authentic material,[7] $[\alpha]^{25}D$ +105.7 (*c* 1.2, 0.1 *N* NaOH) [lit.[1] mp 238–240°, $[\alpha]^{25}D$ +92° (0.1 *N* NaOH)]. The antimicrobial properties of the synthetic material are also essentially identical with those reported[1] for the natural product.



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(7) We thank Dr. J. Berger of our Microbiology Department for making available a small amount of this material which he had obtained from the Upjohn Co. for his own use.

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Thallium in Organic Synthesis. XV. Synthesis of Phenols and Aromatic Nitriles[1,2]

Sir:

We have recently reported[3] a simple, one-step synthesis of aromatic iodides which utilizes the *in situ*

(1) We gratefully acknowledge partial support of this work by the

(1) L. J. Hanka, M. B. Bergy, and R. B. Kelly, *Science*, **154**, 1667 (1967); L. J. Hanka, L. M. Reineke, and D. G. Martin, *J. Bacteriol.*, **100**, 42 (1969); (a) S. H. Rubin and J. Scheiner, *Arch. Biochem.*, **23**, 400 (1949).

(2) M. W. Goldberg and L. H. Sternbach, U. S. Patent 2,489,235 (1949).

(3) Compounds characterized by melting point gave satisfactory combustion analyses.

(4) K. E. Pfitzner and S. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965).

(5) W. S. Wadsworth and W. D. Emmons, *ibid.*, **83**, 1733 (1961).

(6) See C. A. Grob and P. W. Schiess, *Angew. Chem.*, **79**, 1 (1967).

formation of arylthallium ditrifluoroacetates. These latter intermediates are prepared by treatment of the aromatic substrate with thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA);[4] dilution of the reaction mixture with aqueous potassium iodide at room temperature produces the aromatic iodide in high yield. We now describe the utilization of these arylthallium ditrifluoroacetates for the synthesis of phenols and aromatic nitriles.

Phenols. The introduction of a hydroxyl group into benzenoid compounds is, by classical methods, a circuitous sequence of substitution and replacement reactions.[5] We report a new phenol synthesis which may be carried out in a single step, does not require the presence of activating groups, and is subject to control of isomer orientation.[2] Thus, the aromatic compound to be hydroxylated is first thallated under previously described conditions,[4] and to the arylthallium ditrifluoroacetate (which may be isolated and purified at this stage[4] or treated *in situ*) in TFA is added a solution of 1 equiv of lead tetraacetate in TFA. The mixture is stirred at room temperature[6] for 10–25 min, 1 equiv of triphenylphosphine added, excess TFA removed by evaporation, and 6 *N* HCl added to precipitate lead(II) and thallium(I) chlorides. The aryl trifluoroacetate is hydrolyzed with dilute base and the phenol isolated by normal extraction techniques. Representative conversions are summarized in Table I.

Table I. Synthesis of Phenols

$$ArH \xrightarrow{TTFA} ArTl(OOCCF_3)_2 \xrightarrow[2.\ P(C_6H_5)_3]{1.\ Pb(OOCCH_3)_4} (ArOOCCF_3) \xrightarrow[NaOH]{dilute} ArOH$$

Substrate	Product	Yield, %[a]
Toluene	*p*-Cresol	62
o-Xylene	*o*-4-Xylenol	78
m-Xylene	*m*-4-Xylenol	70
p-Xylene	*p*-2-Xylenol	68
p-Cymene	Carvacrol	39
Anisole[b]	4-Hydroxyanisole	41
Chlorobenzene[c]	4-Chlorophenol	56

[a] Yields refer to the hydroxylation step on the isolated arylthallium ditrifluoroacetate intermediate. Yields in the thallation reaction are >90% and are detailed in ref 4. [b] In this case only, omission of triphenylphosphine resulted in a higher yield of the phenol and in a cleaner reaction. [c] The hydroxylation step is carried out under N_2 for 20 min at 73° rather than at room temperature.

The direct synthesis of carvacrol from *p*-cymene in >99% isomer purity illustrates not only the synthetic efficiency of this new hydroxylation procedure, but also the positional control which can be exercised over electrophilic thallation by steric factors.[7]

The above reaction conditions were conceived in the expectation that metal–metal exchange[8] might lead to an intermediate aryllead compound which might be expected to be less stable[9] than the organothallium starting material. The anticipated displacement product from the metal–metal exchange would be TTFA; the triphenylphosphine was added as a specific reducing agent, since TTFA is known to be an efficient oxidizing agent for phenols.[10] We cannot comment further at this time, however, on the detailed mechanism of this reaction except to point out that there is no evidence to suggest a radical process. Further work in progress should clarify whether an aryllead intermediate is actually involved.

Aromatic Nitriles. Replacement of the trifluoroacetoxy groups in arylthallium ditrifluoroacetates by a variety of anions takes place readily in aqueous solution, and in this way compounds of the type $ArTlX_2$ may be prepared.[11] Their utility in synthesis is a function of the strength of the Tl–X bond; $ArTlI_2$ compounds, for example, decompose spontaneously to give aryl iodides.[3,12]

Treatment of arylthallium ditrifluoroacetates with an excess of aqueous potassium cyanide leads to the formation *in situ* of the complex ions $[ArTl(CN)_3]^-K^+$.[13] Our preliminary attempts to convert these complex ions to aromatic nitriles were not promising; pyrolysis either of the complex ions themselves or of the derived arylthallium dicyanides under a variety of conditions gave only traces of aromatic nitriles, indicating a relatively stable Tl–CN bond. However, *photolysis* of an aqueous solution of the above complex ions in the presence of excess potassium cyanide readily gave aromatic nitriles. For example, a 1% solution of *o*-methoxymethylphenylthallium ditrifluoroacetate in water containing 25 equiv of potassium cyanide was photolyzed (Rayonet Photochemical Reactor, 253.7 nm lamps) for 2.5 hr. Extraction of the resulting orange solution with hexane, drying of the extracts, and evaporation gave *o*-cyanobenzyl methyl ether in 55% yield.

Other arylthallium ditrifluoroacetates gave analogous results when photolyzed in excess aqueous potassium cyanide. Representative conversions are summarized in Table II.

All available evidence points to a radical mechanism for this photochemical reaction. Photolysis of phenylthallium ditrifluoroacetate in the presence of smaller amounts of cyanide ion gave traces of benzene, biphenyl, several cyanobiphenyls, and phenol. Furthermore, the formation of *o*-tolunitrile from phenylacetic acid

Smith Kline and French Laboratories, Philadelphia, Pa., and Eli Lilly and Co.

(2) Part XIV: E. C. Taylor, F. Kienzle, R. L. Robey, and A. McKillop, *J. Amer. Chem. Soc.*, **92**, 2175 (1970).

(3) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2427 (1969).

(4) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *ibid.*, 2423 (1969).

(5) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amsterdam, 1965; direct hydroxylation (with peracids) is possible only with substrates strongly activated toward electrophilic substitution.

(6) With some compounds heating is required; see Table I.

(7) Carvacrol as previously synthesized from *p*-cymene has always been contaminated with substantial amounts of thymol (see, for example, W. Strubell and H. Baumgärtel, *Arch. Pharm.*, **291**, 66 (1958)).

(8) R. Criegee in "Oxidation in Organic Chemistry," Vol. A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, pp 363–365.

(9) H. Shapiro and F. W. Frey, "The Organic Compounds of Lead," Wiley, New York, N. Y., 1968.

(10) A. McKillop, B. P. Swann, M. J. Zelesko, and E. C. Taylor, *Angew. Chem. Int. Ed. Engl.*, **9**, 74 (1970).

(11) A. McKillop, J. D. Hunt, and E. C. Taylor, to be published.

(12) It is not possible to prepare phenols by treatment of arylthallium ditrifluoroacetates with hydroxide ion; the products of such reactions are stable arylthallium oxides.

(13) The formation of these complex ions from the reaction of phenylthallium dichloride and potassium cyanide was described by Challenger (F. Challenger and O. V. Richards, *J. Chem. Soc.*, 405 (1934)), who observed that heating of this complex ion in water gave diphenylthallium cyanide.

Table II. Synthesis of Aromatic Nitriles

$$ArH \xrightarrow{TTFA} ArTl(OOCCF_3)_2 \xrightarrow[h\nu]{\text{aqueous KCN}} ArCN$$

Substrate	Product	Yield, %[a]
Toluene	*p*-Tolunitrile	50[b]
Ethylbenzene	*p*-Cyanoethylbenzene	80[c]
o-Xylene	4-Cyano-*o*-xylene	53
m-Xylene	4-Cyano-*m*-xylene	27
p-Xylene	2-Cyano-*p*-xylene	46
Anisole	*p*-Cyanoanisole	70[d]
Benzyl methyl ether	*o*-Cyanobenzyl methyl ether	55
Phenylacetic acid	*o*-Tolunitrile	33

[a] Yields refer to the photolysis step. Yields in the thallation reaction are >90% and are detailed in ref 4. [b] The crude product contained 3% of the *ortho* isomer and 2% of the *meta* isomer, arising from the presence of the corresponding amounts of the *ortho* and *meta* isomers in the intermediate *p*-tolylthallium ditrifluoroacetate. [c] The crude product contained traces of the *meta* (3%) and *ortho* (1%) isomers. [d] The crude product contained 87% *p*-cyanoanisole and 13% *o*-cyanoanisole. One recrystallization gave the pure *para* isomer, mp 59°.

is in agreement with previous observations on the photochemically induced radical decomposition of thallium(III) phenylacetate.[14]

(14) J. K. Kochi and T. W. Bethea, III, *J. Org. Chem.*, **33**, 75 (1968).

An important feature of both the phenol and the aromatic nitrile syntheses herein described is that the hydroxyl and cyano substituents enter the aromatic ring at the point of former attachment of the thallium atom. Clear evidence for this conclusion comes from a comparison of the isomer distributions of aryl iodides with the phenols and nitriles prepared from the same organothallium precursor. Since the position of thallation in a substituted benzene can be controlled,[2] the sequential processes of thallation followed by (a) treatment with lead tetraacetate followed by triphenylphosphine or (b) photolysis in aqueous potassium cyanide make possible the preparation of specifically substituted phenols and aromatic nitriles, respectively.

(15) On leave from the University of South Africa. A grant from the Ernest Oppenheimer Memorial Trust and a travel grant from the C.S.I.R. (South Africa) are gratefully acknowledged.

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Additions and Corrections

Pentacyclodecane Chemistry. VI. Acetolysis and Formolysis of Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-*d*-*syn*-6-yl Tosylate. Evidence for a Symmetrical Intermediate [*J. Amer. Chem. Soc.*, **91**, 3404 (1969)]. By WENDELL L. DILLING, RAYMOND A. PLEPYS, and ROGER D. KROENING, Edgar C. Britton Research Laboratory, The Dow Chemical Company, Midland, Michigan 48640.

On page 3404, ref 1 should read *J. Org. Chem.*, **34**, 2605 (1969).

On page 3405, the equation in footnote 12 should read: $k_1 = {}^1/_2[k_2 - (\ln x)/t]$.

Linear Enthalpy–Spectral Shift Correlations for 1,1,1,3,3,3-Hexafluoro-2-propanol [*J. Amer. Chem. Soc.*, **91**, 4019 (1969)]. By K. F. PURCELL J. A. STIKELEATHER, and S. D. BRUNK, Departments of Chemistry, Kansas State University, Manhattan, Kansas 66502, and Wake Forest University, Winston-Salem, North Carolina.

Equation 4 should read

$$\frac{A_0B_0v}{Q'} = \frac{B_0}{\Delta H} + \frac{1}{K\Delta H} \qquad (4)$$

The entry for triethylamine in Table II should read as follows.

Base	Solvent	A_0,[a] *M*	B_0, *M*	*v*, ml	$-Q'$, kcal
Triethylamine	C_6H_{14}	0.01921	0.04173	201.2	42.91
		0.01902	0.1144	203.3	43.82
		0.01889	0.1596	204.6	44.10

Dichlorocarbene, Free or Complexed? Relative Reactivities of Free CCl_2 [*J. Amer. Chem. Soc.*, **91**, 6035 (1969)]. By P. S. SKELL and M. S. CHOLOD, Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802.

In Table I isobutylene–tetramethylene should read tetramethylene–isobutylene. The following should be added to Table I.

Olefin pair	Reaction temp, °C	Olefin ratio	Dichlorocyclopropane ratio	*k*/*k*
cis-2-Butene–isobutylene	−127 ± 3	7.20[a]	1.28 ± 0.10	0.178 ± 0.03
cis-2-Butene–isobutylene	−152 ± 3	7.20[d]	1.00 ± 0.10	0.139 ± 0.02