decarboxylation of acids formed *in situ* according to the scheme outlined in footnote 4.

Strong evidence for the involvement of free aryl radicals is provided by the relative amounts of the isomeric nitrobiphenyls formed from benzoic acid and nitrobenzene. When the isomer percentages found by phenylating nitrobenzene at 125° with a number of homolytic reagents[2] are corrected to 175° by the method of Williams,[3] the results are in excellent agreement with those found at 170–180° using the homolytic decarboxylation technique. Moreover, we find that the mixture of dichlorobiphenyls produced by phenylating *o*-dichlorobenzene with benzoyl peroxide at 136–142° contains 64% of the 2,3-isomer, a result which again corresponds to the isomer composition obtained using benzoic acid as the phenylating agent.

TABLE I

SYNTHESIS OF BIARYLS BY HOMOLYTIC DECARBOXYLATION[a]

Acid	Solvent	DTBP,[b] moles	Co^{+2},[c] (g. at.) $\times 10^3$	Biaryl yield,[d] %
Benzoic	o-$Cl_2C_6H_4$	0.42	5.1	36[e]
Benzoic	o-$Cl_2C_6H_4$	.46	1.0	20[e]
Benzoic	o-$Cl_2C_6H_4$	.003	1.0	0.5[e]
Benzoic	o-$Cl_2C_6H_4$	.39	0.0	3[e]
Benzoic[f]	o-$Cl_2C_6H_4$	.14	0.0	0.2[e]
Benzoic	$C_6H_5NO_2$	.42	5.1	10[g]
p-Toluic[h]	o-$Cl_2C_6H_4$	.40	1.0	5[i]

[a] 170–180°, 7.0 hr., 0.20 mole acid, 200 ml. solvent, 30 ± 3 l./hr. (unc.) of oxygen. [b] Total di-*t*-butyl peroxide charged. [c] Added as commercial cobaltous naphthenate containing 6% cobalt. [d] Based on acid charged. Unless otherwise noted, yields and isomer percentages were determined by gas chromatography using pure compounds for calibration. [e] Mixtures of 2,3- and 3,4-dichlorobiphenyl containing 65 ± 2% of the former isomer. [f] Experiment performed at 130–140°. [g] Mixture containing 57 ± 1%, 15 ± 1%, and 28 ± 1% of 2-, 3-, and 4-nitrobiphenyl, respectively. [h] 14.0 hr. reaction time. [i] Isolated yield of 2′,3′-dichloro-4-biphenylcarboxylic acid (I). Other products included terephthalic acid (46% yield), 3′,4′-dichloro-4-biphenylcarboxylic acid (II), and (possibly) methyldichlorobiphenyls and methyldichlorobiphenyl carboxylates. Proofs of structure for I and II will be deferred to a later publication.

Not the least remarkable feature of homolytic decarboxylation is that thus far no evidence has been obtained for the formation of products (*e.g.*, phenols) which might reasonably be expected to arise from the reaction of aryl radicals with oxygen.[4] This observation is of particular interest in view of a recent suggestion by Hammond and Nandi[5] that such reactions may be much slower than was formerly believed.

Of the possible mechanisms envisioned for homolytic decarboxylation, the most likely would appear to be those involving loss of carbon dioxide from transient aroyloxy radicals. Aroyloxy might be formed by reaction of the starting acid with cobaltic ion or, more strikingly, by free-radical abstraction of hydrogen from the acid O-H bond.[6] Although the latter course has no well-established precedent,[7] it appears to be the most satisfactory way of explaining the uncatalyzed reaction (assuming, of course, that adventitious traces of cobalt were not present under these conditions). It should be noted that some aliphatic acids also have been reported recently to undergo oxidative decarboxylation under conditions which should favor a homolytic process.[8]

Further work on various mechanistic and synthetic aspects of homolytic decarboxylation is in progress.

It is a pleasure to acknowledge the able technical assistance of Mr. H. J. Tarski and numerous other members of the Research and Development Division. Considerable thanks are due Dr. R. H. Perry, Jr., for his enthusiastic interest and support.

(2) D. H. Hey, C. J. M. Stirling and G. H. Williams, (a) *J. Chem. Soc.*, 2747 (1954); (b) 1475 (1956).

(3) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, Inc., New York, N. Y., 1960, pp. 9–11.

(4) This negative result may be at least partly due to low concentrations of oxygen in the liquid phase. In fact, in many experiments it appeared that all of the methyl radicals derived from di-*t*-butyl peroxide were not trapped by oxygen. In these cases appreciable methylation of the aromatic solvent occurred, forming substituted toluenes which were then oxidized in part to the corresponding benzoic acids.

(5) G. S. Hammond and U. S. Nandi, *J. Am. Chem. Soc.*, **83**, 1213 (1961).

(6) Cobaltic ion appears to react with substrates containing O–H bonds (*e.g.*, formic acid, alcohols): $XOH + Co^{+3} \rightarrow XO\cdot + H^+ + Co^{+2}$. See C. E. H. Bawn and A. G. White, *J. Chem. Soc.*, 331, 339, 343 (1951). For the radical abstraction mechanism, the catalytic effect of cobalt might be rationalized in terms of radical-forming reactions involving alcoholic by-products and/or intermediate hydroperoxides. See C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 427–428, and references therein. However, *t*-butoxy and methyl radicals derived from DTBP apparently do not attack the CO_2H group, since homolytic decarboxylation does not occur in the absence of oxygen. Two possible explanations of the effect of oxygen are that (a) the methyl hydroperoxide formed in its presence[1] oxidizes cobaltous ion to the active cobaltic state, and that (b) methylperoxy radicals can abstract hydrogen from the acid O–H bond.

(7) However, evidence recently has been cited for free-radical abstraction of hydrogen from the O–H bond of cyclopropanols [C. H. DePuy, G. M. Dappen and J. W. Hausser, *J. Am. Chem. Soc.*, **83**, 3156 (1961)] and from the carboxyl group of capric acid, I. W. Berezin, Symposium on "Autoxidation and Cumol-phenol Synthesis," Leuna, Germany, September, 1960.

(8) (a) R. van Helden, A. F. Bickel and E. C. Kooyman, *Rec. trav. chim.*, **80**, 1257 (1961); (b) E. A. Blair and J. J. Melchiore, U. S. Patent 3,013,038 (1961).

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SIMULATION OF THE BIOSYNTHESIS OF TETRACYCLINES. A PARTIAL SYNTHESIS OF TETRACYCLINE FROM ANHYDROAUREOMYCIN

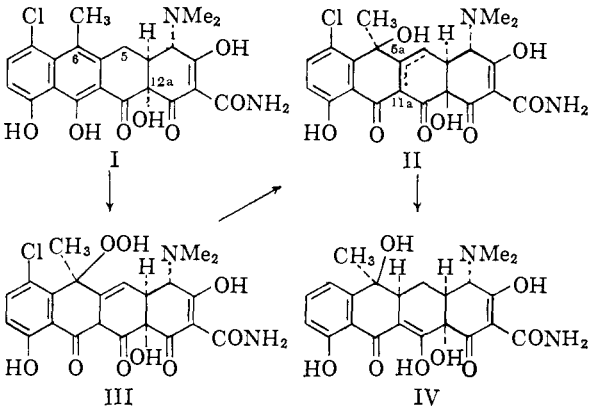
Sir:

An important late step in the biosynthesis of the tetracycline antibiotics, whose skeletons are largely evolved from head-to-tail linkage of "acetate" units,[1] is the introduction of hydroxyl functions at positions 5, 6 and 12a.[2] The mechanism of biochemical hydroxylation at position 6 merits particular attention in view of the isolation of 7-chloro-

(1) A. J. Birch, J. F. Snell and P. J. Thomson, *J. Chem. Soc.*, 425 (1962).

(2) For recent laboratory analogies for 12a-hydroxylation of the corresponding deoxytetracyclines see (a) H. Muxfeldt and A. Kreutzer, *Naturwissenschaften*, **46**, 214 (1959) (perbenzoic acid); (b) C. E. Holmund, W. W. Andres and A. J. Shay, *J. Am. Chem. Soc.*, **81**, 4748 (1959) (sodium nitrite); (c) **81**, 4750 (1959) (microbiological method); (d) H. Muxfeldt, G. Buhr and L. Bangert, *Angew. Chemie* (Internat. Edn.), **1**, 157 1962) (platinum/oxygen).

5a(11a)-dehydrotetracycline[3] (II, Δ5a,11a) from a mutant of *Streptomyces aureofaciens* and the demonstration that this metabolite is a precursor of 7-chlorotetracycline.[4] Consideration of structure (II) led us to favor 7-chloroanhydrotetracycline (I) as the biological progenitor of (II)[5]; enzymic oxidation of (I) could produce (II) directly or involve formation of an intermediate 6-hydroperoxide[6] (III).

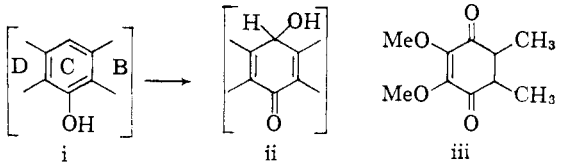


We now have found that this phase of the proposed biosynthesis may be simulated in the laboratory by photo-oxygenation[7] of 7-chloroanhydrotetracycline (I). Thus, after passage of oxygen through a benzene solution (0.25%) of (I) irradiated with light from a fluorescent lamp for 5 days, a yellow crystalline solid (yield, after recycling, 70%) appeared on the walls of the Pyrex vessel. The *major* component of this mixture (crystallized from chloroform) is 7-chloro-6-deoxy-6-hydroperoxy-5,5a-dehydrotetracycline (III) (calcd. for $C_{22}H_{21}N_2ClO_9$: C, 53.64; H, 4.30; N, 5.69. Found: C, 53.38; H, 4.11; N, 5.68) giving a positive ferrous thiocyanate reaction[8] and having light absorption (λ_{max} 249 mμ, ε 24,100; 375–380 mμ, ε 4,500 [in methanolic 0.1 *N* HCl]; γ_{CHCl_3} 3608, 3467, 1707, 1640, 1600 cm.$^{-1}$) virtually identical with that of (II).[9] The stereochemistry of (III) proved to be the "natural" one,[10] for catalytic reduction (1 mole H_2; Pd-C (5%); MeOH) afforded quantitatively the free base of 7-chlorodehydrotetracycline (II), $[\alpha]_D$ + 210° (*c*, 0.4 in $CHCl_3$) identical in every respect (ultraviolet, infrared spectra) with the *S. aureofaciens* metabolite,[11] $[\alpha]_D$ + 212° (*c*, 0.38 in $CHCl_3$). We wish to suggest that the strong carbonyl absorption at 1711 cm.$^{-1}$ in this compound favors the 5,5a- rather than the 5a,11a-location of the double bond. The reduction of (II) to tetracycline (IV) already has been described[3] and completes the partial synthesis. With the impending convergence[12] of the efforts of several laboratories on stereospecific syntheses of diverse anhydrotetracyclines, the present reaction sequence offers a solution[13] to the total stereospecific synthesis of all of the tetracycline antibiotics, as well as providing the impetus for appropriate radiochemical incorporation studies.

(3) J. R. D. McCormick, P. A. Miller, J. A. Growich, N. O. Sjolander and A. P. Doerschuk, *J. Am. Chem. Soc.*, **80**, 5572 (1958).

(4) J. R. D. McCormick, N. O. Sjolander, P. A. Miller, U. Hirsch, N. H. Arnold and A. P. Doerschuk, *ibid.*, **80**, 6460 (1958).

(5) In an alternative hypothesis (ref. 1) the 5a,11a-double bond marks the site of an aldol condensation implying that 6-hydroxylation occurs without involvement of an aromatic ring C. In the case of 6-demethyltetracycline this may seem at first sight preferable to quinol formation from a phenol unsubstituted in the *para*-position (i) → (ii). However, the isolation of the keto-form of a phenol is not without precedent, *e.g.*, gliorosein (iii) (E. B. Vischer, *J. Chem. Soc.*, 815 (1953)).

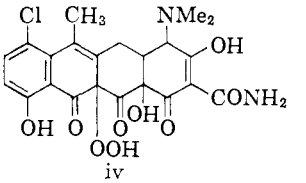


(6) S. Goodwin and B. Witkop, *J. Am. Chem. Soc.*, **79**, 179 (1957), have suggested the possible intervention of a quinol hydroperoxide in homogentisic acid biosynthesis.

(7) See A. G. Davies, "Organic Peroxides," Butterworths, London, 1961.

(8) F. Feigl, "Spots Tests in Organic Analysis," 6th Edn., Elsevier, London, 1960, p. 535.

(9) The intact nature of the *enolizable* (but not fully enolized) 10,11,12-trioxygenated B-C-D-chromophore was revealed by a characteristic bathochromic shift of the long wave length band of the spectrum of (III) to 410 mμ in the presence of Ni^{2+} ion [see L. H. Conover, *Chem. Soc. Special Publications*, 5, 48 (1956)]. This served to eliminate alternatives such as (iv)



(10) The nature of the minor product and of the stereoselectivity of this reaction will be discussed in the publication.

(11) We are indebted to Drs. J. R. D. McCormick and S. Kushner (Lederle Laboratories, Pearl River, N. Y.) for a sample of 7-chlorodehydrotetracycline.

(12) See *e.g.*, H. Muxfeldt, *Chem. Ber.*, **92**, 3122 (1959); A. S. Kende, T. L. Fields, J. H. Boothe and S. Kushner, *J. Am. Chem. Soc.*, **83**, 439 (1961).

(13) Studies of the photo-oxygenation of other anhydrotetracyclines are in progress.

(14) Pfizer Ltd. Predoctoral Fellow, 1960–1962.

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RECEIVED MAY 1, 1962

A NEW REARRANGEMENT OF α-AMINOKETONES

Sir:

We wish to report the discovery of a novel skeletal rearrangement of α-aminoketones. An example of this rearrangement is the conversion of 2-ethyl-2-methylaminobutyrophenone (Ia) to 3-methylamino-3-phenyl-4-hexanone (IIa) in 35% yield at 240°. Similarly, Ib could be rearranged to IIb in 32% yield. The scope of the reaction was shown to include aliphatic aminoketones by the 32% conversion of α-methylaminocyclopentyl methyl ketone (V) to 2-methyl-2-methylaminocyclohexanone (VI), which rearrangement involved ring enlargement.

A mechanism for this rearrangement is proposed which involves two carbon skeleton migrations. In the rearrangement of Ia, for example, the iminoalcohol III is considered to be an intermediate resulting from the migration of an ethyl group,