in cases for which x is real. We obtain, then, the formulae 2–5.

These formulae are valid for particles of spherical form, in which case $x = 2$[1]. They are valid also if the form is non-spherical, provided the particles are all oriented in the same direction. If the particles are ellipsoids (half axis: a, b, c) the value of x can be obtained in a similar manner to that used earlier in treating the case of random orientation[2]. When a is perpendicular to the electrodes, the solution is:

$$x = \frac{2 - abcL_a}{abcL_a}$$

where

$$L_a = \int_0^\infty \frac{d\lambda}{(a^2+\lambda)\sqrt{(a^2+\lambda)(b^2+\lambda)(c^2+\lambda)}}.$$

The Figure records x for ellipsoids of revolution of different axis ratios, arranged with the axis of revolution either parallel with or perpendicular to the electrodes. A limiting case is that of cylinders arranged parallel to the electrodes, for which $x = 1$.

In the ultrahigh frequency range of particular biological interest, the effect of the conductances is small and we have then:

$$\sigma_2/\sigma_1 = \frac{C(\varepsilon\,\varepsilon_1)}{D(\varepsilon\,\varepsilon_1)} + \frac{(x+1)^2\,\varrho\,\varepsilon_1^2\,(\sigma/\sigma_1 - \varepsilon/\varepsilon_1)}{[D(\varepsilon\,\varepsilon_1)]^2}; \qquad (7)$$

$$\varepsilon_2/\varepsilon_1 = \frac{C(\varepsilon\,\varepsilon_1)}{D(\varepsilon\,\varepsilon_1)}. \qquad (8)$$

Since now x depends on $\varepsilon_2/\varepsilon_1$ only and therefore is real, these formulae are valid also for non-spherical particles of random orientation. For ellipsoids, the value of x can be calculated by means of the formulae given earlier[2], using $k_2/k_1 = \varepsilon_2/\varepsilon_1$. This paper gives also numerical values of x in graphical form for ellipsoids of rotation of different axis ratios and different values of $k_2/k_1 = \varepsilon_2/\varepsilon_1$.

Examination of formulae (2) and (3) will show that, whether $\varepsilon_2/\varepsilon_1 \lessgtr \sigma_2/\sigma_1$, ε decreases and σ increases with increasing frequency (σ_p and ε_p of the two phases being taken to be independent of frequency) and the curves representing $(\sigma/\sigma_1)\ n = \infty/(\sigma/\sigma_1)\ n = 0$ and $(\varepsilon/\varepsilon_1)\ n = 0/(\varepsilon/\varepsilon_1)\ n = \infty$ plotted against $\varepsilon_2/\varepsilon_1$ (or σ_2/σ_1) for a fixed value of σ_2/σ_1 (or $\varepsilon_2/\varepsilon_1$) have a minimum at $\varepsilon_2/\varepsilon_1 = \sigma_2/\sigma_1$, where the two quantities are unity. (These statements follow also directly from the well known theorem, that the lines of electric force through a conducting heterogeneous system, are distributed in such a manner that the energy consumed is minimum.) When the difference between $\varepsilon_2/\varepsilon_1$ and σ_2/σ_1 is not very large, the error resulting from calculating the electric conductivity of the suspension by means of formula (1), is therefore relatively small.

In the earlier calculations (from ultrahigh frequency observations) of the interior conductivity of the red blood cell[3] which were carried out in this manner, the greatest difference between $\varepsilon_2/\varepsilon_1$ and σ_2/σ_1 —which in this case represent the ratios of respectively dielectric constants and conductivities of cell interior to those of suspending fluid—was only about 10% (for corpuscles in plasma), and the values given require corrections of less than 2% from the standpoint of the present theory.

H. FRICKE

Walter B. James Laboratory of Biophysics, Biological Laboratory, Cold Spring Harbor, New York, May 8, 1952.

Zusammenfassung

Es wird darauf hingewiesen, dass die Formel

$$\frac{k-k_1}{k+xk_1} = \varrho\,\frac{k_2-k_1}{k_2+xk_1}$$

(k: dielektrische Konstante bzw. Leitfähigkeit) für die elektrischen Eigenschaften einer Suspension auch dann gilt, wenn die k komplex sind. Verschiedene Anwendungen dieser verallgemeinerten Formel werden besprochen, die für elektrische Messungen an zellularen Substraten biologischer Herkunft bei Ultrahochfrequenzen von Interesse sind. Diese umfassen Suspensionen orientierter Rotationsellipsoide. In Weiterführung früherer Arbeiten[1] werden Kurven angegeben, die x für solche Systeme darstellen.

[1] H. FRICKE, Phys. Rev. *24*, 575 (1924); Physics *1*, 106 (1931).

Significance and Rearrangements of Quinol Models of Tyrosine Metabolites[1]

Labile metabolites in the breakdown of amino acids are of fundamental interest[2]. The transformation of tyrosine to homogentisic acid involving the apparent migration of an acetic acid side chain has led the biochemists to the assumption of a *labile quinol intermediate* as early as 1907[3]. The oxidation of p-alkylphenols with CARO's acid offers welcome analogies to the biochemical oxidation of tyrosine. Whereas under neutral conditions (in the presence of $MgCO_3$) p-cresol is converted to p-toluquinol[4] (yield, 5–10%, possibly some o-hydroxylation to *homo*-catechol) the oxidation in acidic medium (1·8N H_2SO_4)[5] leads directly to toluhydroquinone (about 15%, no catechol). These results prompted FRIEDMAN[3], NEUBAUER[6], and DAKIN[7] to attempt unsuccessfully the preparation of quinols corresponding to tyrosine (DAKIN), p-hydroxyphenylpyruvic (NEUBAUER) and p-hydroxyphenylacetic acids (FRIEDMANN, DAKIN). Our own ex-

[1] J. C. MAXWELL, *Treatise on Electricity and Magnetism* (Clarendon Press, Oxford, 1937), p. 313.

[2] H. FRICKE, Phys. Rev. *24*, 575 (1924); Physics *1*, 106 (1931).

[3] B. RAJEWSKY and H. SCHWAN, Naturwissenschaften *35*, 315 (1948). – H. F. COOK, Nature *168*, 247 (1951).

[1] *On the Mechanism of Oxidation.* VII. Preceding paper in this series: Ber. dtsch. chem. Ges. *85*, 3. H. WIELAND, Festschrift (1952).

[2] Cf. Paper V in this series: Exper. *8*, 36 (1952).

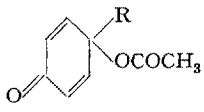
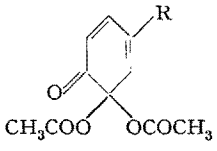
[3] E. FRIEDMANN, Beitr. chem. Physiol. Pathol. *11*, 304 (1908). – In 1901, E. MAYER [Dtsch. Arch. Klin. Med. *70*, 443 (1901)] called attention to the similarity of the reaction tyrosine → homogentisic acid to the rearrangement of p-tolylhydroxylamine to toluhydroquinone [E. BAMBERGER, Ber. dtsch. chem. Ges. *28*, 245 (1895)], at a time when the isolation of the intermediate quinol had not been reported yet by BAMBERGER [Ber. dtsch. chem. Ges. *33*, 3600 (1901)].

[4] E. BAMBERGER, Ber. dtsch. chem. Ges. *36*, 2028 (1903).

[5] T. KUMAZI and R. WOLFFENSTEIN, Ber. dtsch. chem. Ges. *41*, 297 (1908).

[6] O. NEUBAUER, Dtsch. Arch. Klin. Med. *95*, 211 (1909).

[7] H. D. DAKIN, J. Biol. Chem. *8*, 13 (1910). In the light of these precedents, it is surprising to find the following statement by DAKIN in his book *Oxidation and Reduction in the Animal Body* (Longmans, Green & Co., London, New York, Toronto, 1922), p. 93: "The Chemical analogy for the wandering of the $-CH_2-CO-COOH$ group is lacking". The recent findings by S. WEINHOUSE and R. H. MILLINGTON, J. Biol. Chem. *175*, 995 (1948) and by B. SCHEPERTZ and S. GURIN, ibid. *180*, 663 (1949), using tyrosine labeled with C_{14} in various positions, are clear evidence of the intramolecular migration of the side chain.

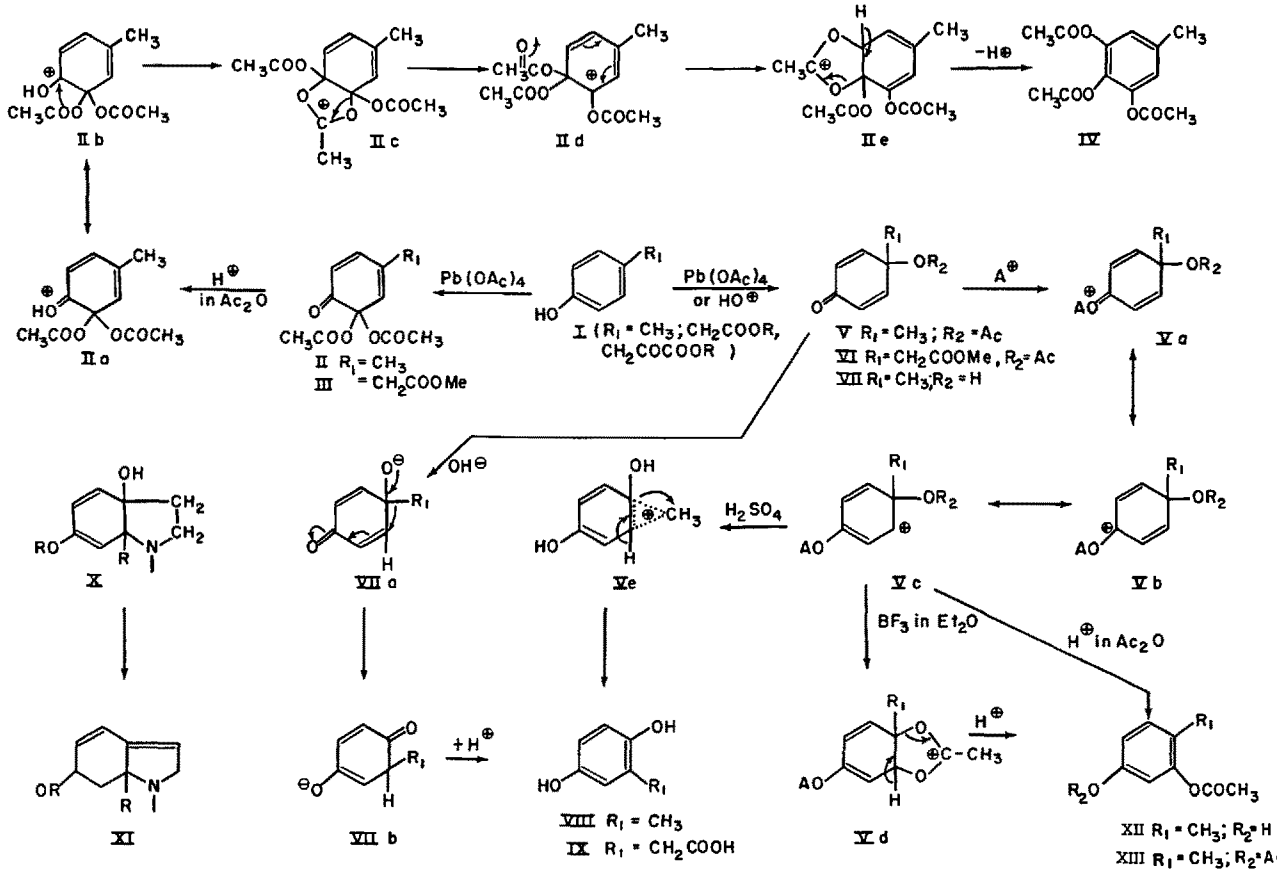
Formula	Compound	Melting point	IR-Absorption (in microns)			UV-Absorption (in EtOH) λ max (logε)
			ester bands	Conj. CO	Conj. F	
	V (R=CH_3)	42°	5·67–5·74	5·98	6·11	236 mμ (4·16) (*a*)
	VI (R=CH_2–COOMe)	oil	5·74	5·96	6·11	228 mμ (3·92)
	II (R=CH_3)	141–142°	5·67	5·88	6·01	314 mμ (3·42) (*b*)
	III (R=CH_2–COOMe)	102–104°	5·66–5·72	5·88	6·0	312 mμ (2·76)

(*a*) F. WESSELY [F. WESSELY and F. SINWEL, Mh. Chemie. *81*, 1055 (1950)] observed only end absorption with p-toluquinol acetate. The free p-toluquinol absorbs at somewhat shorter wave length: λ max 227 mμ (logε 4·13), cf. J. LIFSCHITZ *et al.*, Rec. Trav. chim. Pays-Bas *43*, 404 (1924). (*b*) F. WESSELY [F. WESSELY and F. SINWEL, Mh. Chemie *81*, 1055 1950)] gives λ max 312 (logε 3·4).

periments showed again the difficulty of obtaining such quinols by BAMBERGER rearrangement of the parent hydroxylamino derivatives or by peracid oxidation of the substituted phenols. The use of lead tetraacetate in glacial acetic acid, a method recently introduced by WESSELY[1], made it possible for the first time to prepare quinols with side chains such as $R_1 = CH_2$–$COOCH_3$, etc. Methyl p-hydroxyphenylacetate under these conditions gave about 5% of the o-quinone ortho-diacetate III, m. p. 102–104°, and 2–5% of the p-quinol VI. The comparison of the chemical and spectral data (Table) shows the analogy between the quinol acetates from p-cresol[1] and the corresponding compounds from methyl p-hydroxyphenyl acetate. The action of acid on VI would be expected to result in hydrolysis of the two ester groups and in rearrangement to homogentisic acid (IX). However, when such acid-catalyzed rearrangements were studied with the simpler compounds V and II under

[1] F. WESSELY and F. SINWEL, Mh. Chemie *81*, 1055 (1950).

[1] F. WESSELY and F. SINWEL, Mh. Chemie *81*, 1055 (1950).



unhydrous conditions, novel migrations of acetoxy groups were observed.

Four types of rearrangements can now be distinguished in the p-toluquinol acetate series:

(1) An *external addition of acetate anion* to the cation V*c* (arising *via* V*a* ⟷ V*b*) by the action of acetic anhydride in a *sulfuric acid-catalyzed* THIELE *reaction*. The product is (starting with V) diacetyl cresorcinol (XIII, liquid, yield about 70%), hydrolyzed by base to cresorcinol, m. p. 106–107°, identified by analysis, mixed melting point, and IR-spectrum.

(2) An *internal migration of the acetoxy group* by the action of boron trifluoride in ether involving a cyclic carbonium intermediate V*d* reminiscent of similar intermediates in replacement reactions in which complex neighboring groups participate[1]. The reaction product in this case is the new *monoacetyl cresorcinol* (XII, yield 70%), m. p. 102–104°, hydrolyzed to cresorcinol.

(3) Hydrolysis of the p-quinol acetate in aqueous *acidic* solution followed by *migration of the alkyl group* (V*e*) leading to toluhydroquinone (VIII) or to homogentisic acid (IX).

(4) Hydrolysis of the p-quinol acetate in aqueous *alkaline* medium followed by a *benzilic acid type of rearrangement* (VII*a* → VII*b*) leading again to derivatives of hydroquinone (VIII, IX).

When the o-quinone *ortho*-acetate (II) was dissolved in acetic anhydride in the presence of catalytic amounts of sulfuric acid at room temperature an exothermic THIELE reaction of an unusual kind occurred yielding the *triacetyl pyrrogallol* derivative IX, m. p. 101·5–102·5°. One of the possible routes in this, as we believe, combined *intra-* and *intermolecular acetylation process* is pictured in the hypothetical intermediates II*a* → II*e*. IV, on acid hydrolysis, furnished 3,4,5-trihydroxytoluene (m. p. 126–7°) which, after methylation to the liquid 3,4,5-trimethoxytoluene, gave, on oxidation with potassium permanganate in acetone, trimethylgallic acid (m. p. 157°) identified by analysis, mixed melting points and infrared spectra.

To summarize: p-quinol acetates can rearrange to hydroquinone as well as resorcinol derivatives, o-quinoid compounds of type II to pyrrogallol derivatives, whereby no change in the state of oxidation or reduction occurs. The formation of the o-quinoid compound II from I with lead tetraacetate may not necessarily go through the catechol state[2], a consideration which is significant for enzymatic reactions of a similar kind, such as the transformation of 3-hydroxyanthranilic acid to niacin. There 3,4-dihydroxyanthranilic acid, contrary to previous claims[3] is *not* the intermediate[4], but rather the o-quinoid compound (or an open analog[5]).

The quinols derived from p-cresol and hydroxyphenylacetate were not metabolized by the enzyme preparation from rat liver[6] as Dr. LA DU[7] found out. We comment on the negative result of such a test in the same way as FROMHERZ and HERMANNS[1] did forty years ago. Our results on the preparation and rearrangement of quinols with varying side chains derived from phenols I [R_1 = $C_6H_2COCH_3$; CH_2–CH(NHAc)COOR, etc.] will be reported elsewhere. That suitable negative centers of side chains, such as ethanamine, are capable of adding internally to the o-quinoid and p-quinoid systems II and V is known from previous work and considerations[2]. The loss of water from an intermediate such as X would lead to a system XI present in *β*-erythroidine[3] and, presumably in a slightly modified form, also in gliotoxin[4]. Model experiments in this direction are in progress.

B. WITKOP and Miss SIDNEY GOODWIN

National Institutes of Health, Washington 14, D. C., July 28, 1952.

Zusammenfassung

Der Dualismus der o- und p-Hydroxylierung, der beim Tyrosin *in vivo* beobachtet wird, lässt sich *in vitro* mit Bleitetraazetat nach WESSELY an geeigneten p-substituierten Phenolen, wie zum Beispiel p-Oxyphenylessigsäureester, demonstrieren. Die o- und p-Azetoxylierung führt zu Azetaten o- und p-chinoider Verbindungen, die eine Fülle neuartiger säuren- und basenkatalysierter *intra-* und *inter*molekularer Umlagerungen zu Derivaten des Resorzins, Hydrochinons und Pyrrogallols zeigen.

[1] S. WINSTEIN, L. GOODMAN and R. BOSCHAN, J. Amer. Chem. Soc. *72*, 4669 (1950); XII intern. Congr. of Pure and Applied Chemistry, Abstracts Org. Chem., 436, September 1951, New York. Cf. S. WINSTEIN and R. E. BUCKLES, J. Amer. Chem. Soc. *65*, 613 (1943).

[2] Cf. J. N. SMITH, Biochem. Soc. Symposia, *5* 15 (1950).

[3] K. MAKINO, F. ITOH, and K. NISHI, Nature *167*, 115 (1951).

[4] L. M. HENDERSON, H. N. HILL, R. E. KOSKI, and I. M. WEINSTOCK, Proc. Soc. Exp. Biol. Med. *78*, 441 (1951).

[5] A. H. BOKMAN and B. S. SCHWEIGERT, Arch. Biochem. Biophys. *33*, 270 (1951). – Cf. A. BUTENANDT and H. G. SCHLOSSBERGER, Ber. dtsch. chem. Ges. *85*, 565 (1952).

[6] B. N. LA DU, Jr., and D. M. GREENBERG, J. Biol. Chem. *190*, 245 (1951).

[7] We are indebted to Dr. LA DU for these tests. Assaying of further quinols is in progress.

[1] K. FROMHERZ and L. HERMANNS, Z. Physiol. Chem. *91*, 213 (1914).

[2] *D.* RAPER, Biochem. J. *20*, 735 (1926); *21*, 89 (1927). – A. B. LERNER and T. B. FITZPATRICK, Physiological Review *30*, 191 (1950). – Cf. R. ROBINSON, Chemistry and Industry 358 (*1952*).

[3] V. PRELOG *et al.*, Helv. chim. Acta *34*, 1601, 1969 (1951). – V. BOEKELHEIDE, M. F. GRUNDON, and J. WEINSTOCK, J. Amer. Chem. Soc. *74*, 1866 (1952); A. C. S. Meeting, Atlantic City, Sept. 14–19, 1952, Abstracts, 12 M.

[4] Unpublished results on the hydrogenation of gliotoxin by Dr. J. D. DUTCHER (as well as spectrophotometric observations) make the assumption of an aromatic ring in gliotoxin untenable. We are grateful to Dr. DUTCHER for the communication of his results as well as for stimulating discussions.

The Presence of 5-Hydroxytryptamine in the Venom of *Bufo marinus*

Serotonin, the vasoconstrictor substance in mammalian serum, has recently been identified by RAPPORT, GREEN, and PAGE[1] as 5-hydroxytryptamine. RAND and REID[2] have also shown that thrombocytin, the hemostatic agent in platelets, is probably 5-hydroxytryptamine. ERSPAMER and OTTOLENGHI[3] found that enteramine, which serves as a local hormone in the gut, is apparently 5-hydroxytryptamine. They have also found this substance in many invertebrate sources.

JENSEN and CHEN[4] and WIELAND[5], in 1934, established that various N-methyl derivatives of 5-hydroxytryptamine which have considerable pressor activity were present in large amount in toad venom. 5-Hydroxy-

[1] M. M. RAPPORT, A. A. GREEN, and I. H. PAGE, J. Biol. Chem. *176*, 1243 (1948).

[2] M. RAND and G. REID, Nature *168*, 385 (1951).

[3] V. ERSPAMER and A. OTTOLENGHI, Exper. *8*, 31 (1952).

[4] H. JENSEN and K. K. CHEN, J. Biol. Chem. *116*, 87 (1936).

[5] H. WIELAND, Ann. Chem. *513*, 1 (1934).