TRANSFORMATIONS OF 6-METHYLSALICYLIC ACID DERIVATIVES

S. NEELAKANTAN AND T. R. SESHADRI

Department of Chemistry, University of Delhi, Delhi-8

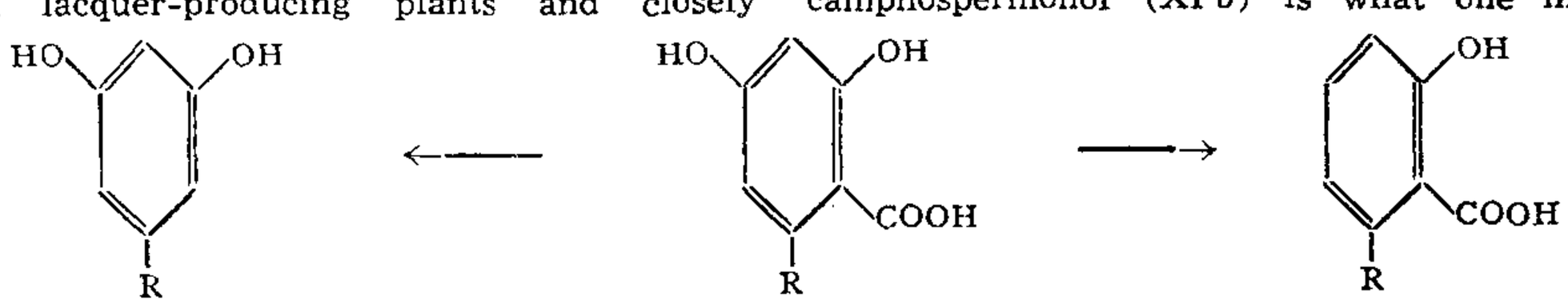
IN earlier publications[1,2] relating to the biogenesis of lichen and mould products, it was indicated that a large number of these fall into the C_8-unit (orsellinic unit) system. Attempts have also been made to derive them from acetic acid units.[3,4] It has been shown that acetate as a nutrient in the growth medium could be utilized by moulds, and acetates may, therefore, play an important part in biogenesis. But, as a guide to the evolution of molecular architecture, the acetate hypothesis may not be so successful. The inherent difficulty is in the smallness of the unit as it is only next to the C_1-unit. Larger units like C_5, C_6 and C_8 provide definitely better indications. The contention of Robinson[5] which is very significant in this connection may be quoted here. "There is no difficulty, for example, in adding atom to atom and thus arriving at any desired structure. In general the simple substances provide no useful comparisons, because the possibilities cannot be distinguished by inspection. On the other hand, the more complex molecules are much more revealing and a study of them soon leads to certain firm convictions. In this way a complex of interrelated ideas is formed and we can build on firmer ground." The significance of the C_8-unit seems to be increasing because of newer discoveries. In our study of the C_8-unit scheme, particular emphasis has been given to the gradual modifications that the C_8-unit has undergone in various situations; these modifications involve reactions which can take place in the concerned structures with facility. In the present paper, the application of the C_8-unit scheme of biogenesis is explained for the 6-methylsalicylic acid derivatives.

A. Benzenoid Derivatives

(*i*) *Anacardic Acid Series.*—These constitute a group of natural products obtained from lacquer-producing plants and closely related to 6-methylsalicylic acid (I). They are anacardic acid (II) (from *Anacardium occidentale*), ginkgolic acid (III) (from *Ginkgo biloba*) and pelandjauic acid (IV) (from *Pentaspadon* spp.).

The evolution of 6-methylsalicylic acid (I), a mould product, has already been discussed.[2,6] It involves the loss of a hydroxyl group of the orsellinic acid (C_8-) unit. The lengthening of the methyl side chain in the 6-position of the C_8-unit by addition of even number of carbon atoms was originally shown to be a common feature in lichen depsides and depsidones[1] and more recently recognized in the benzoquinone series.[7] The above three acids (II, III & IV), which are chain-lengthened analogues of 6-methylsalicylic acid, should have a similar origin. This explanation of the biogenetic relationship receives support from the occurrence in the same sources of orcinol derivatives with lengthened side chains. They are cardol (V) (in *Anacardium occidentale*) and bilobol (VI) (in *Ginkgo biloba*). Orcinol (VII) itself has long been known as a lichen product (*e.g.*, *Roccella montagnei*[8]), produced by facile decarboxylation of orsellinic acid (C_8-unit, VIII). Cardol (V) and bilobol (VI) should be considered to be similar decarboxylation products of the corresponding carboxylic acids (IX & X). Thus from a common orsellinic acid type both the anacardic acid and the cardol groups of compounds can be derived.

(*ii*) m-*Cresol Derivatives.*—Members of the cardanol series (XI *a*) (from *Anacardium occidentale*) and campnospermonol (XI *b*) (from *Campnosperma* spp.) are also related to 6-methylsalicylic acid analogues as decarboxylation products. The presence of the carbonyl group in the β-position of the side chain in campnospermonol (XI *b*) is what one meets



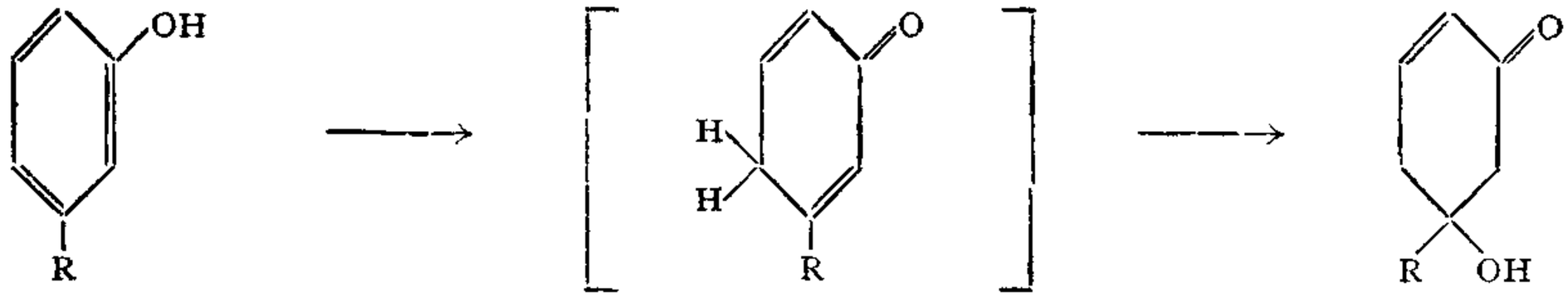
VII, R = CH_3
V, R = $C_{15}H_{27}$
VI, R = $C_{15}H_{29}$

VIII, R = CH_3
IX, R = $C_{15}H_{27}$
X, R = $C_{15}H_{29}$

I, R = CH_3
II, R = $C_{15}H_{27}$
III, R = $C_{15}H_{29}$
IV, R = $C_{17}H_{31}$

with in the lichen acid series also (*e.g.*, physodic acid).

Campnospermonol (XI *b*) is found to be accompanied by an optically active long chain compound[9] (XII) which is a derivative of

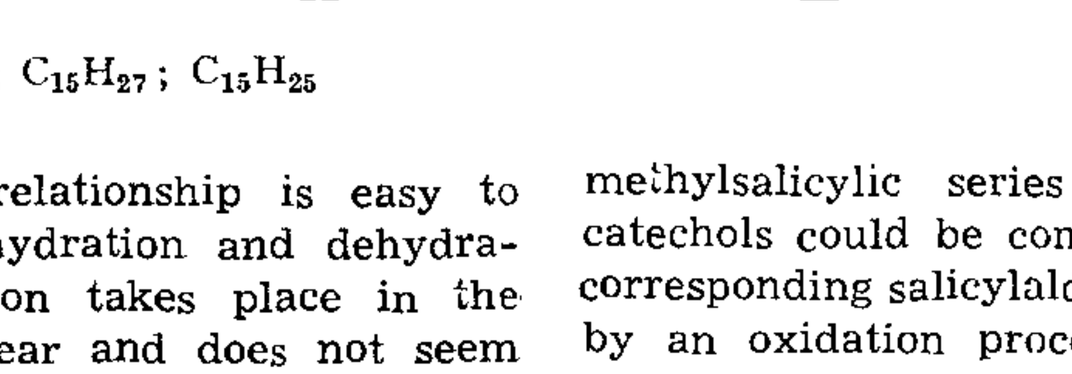


XI *a*, R = $C_{15}H_{31}$; $C_{15}H_{29}$; $C_{15}H_{27}$; $C_{15}H_{25}$
XI *b*, R = $CH_2COC_{17}H_{33}$

XII

cyclohexenone. Their relationship is easy to discern. It is one of hydration and dehydration. But how hydration takes place in the aromatic unit is not clear and does not seem to have known biochemical analogies. A possible course of the reaction is indicated above.

(*iii*) *Quinol Derivatives.*—Another compound occurring along with campnospermonol (XI) is a long chain quinol (XIII) which has



XI *b* XIII

recently been isolated from the oil of *Campnosperma auriculata*.[10] Its relationship to campnospermonol (XI) is simple and its biogenesis should involve an extra step of *para*

XVII

XIV, R = $C_{15}H_{31}$, $C_{15}H_{29}$, $C_{15}H_{27}$, $C_{15}H_{25}$
XV, R = $C_{17}H_{33}$
XVI, R = $C_{17}H_{31}$

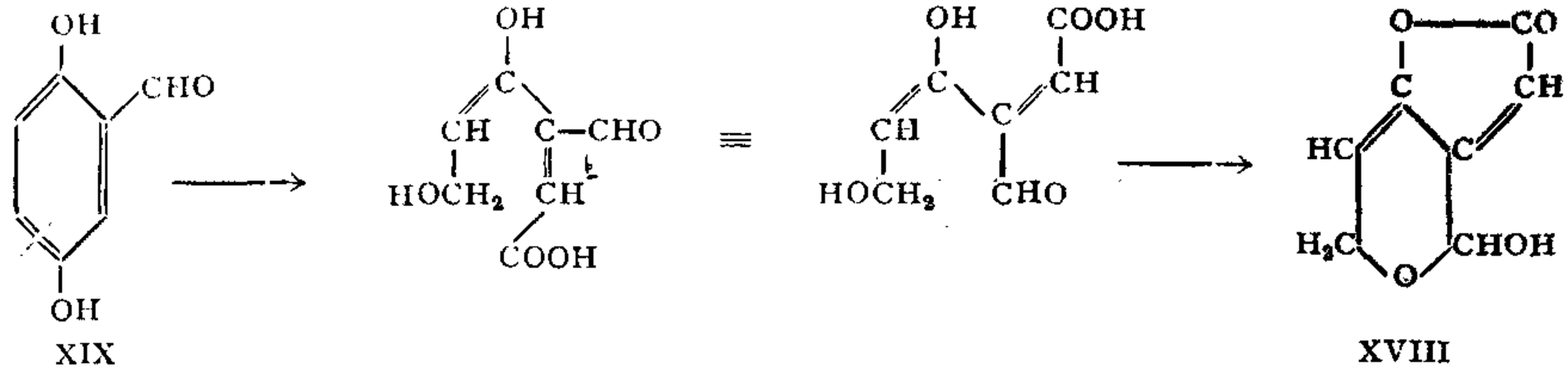
nuclear oxidation besides reduction of the side chain.

(*iv*) *Catechol Derivatives.*—There seems to be a group of compounds which are not directly related to 6-methylsalicylic acid but to the corresponding aldehyde as the C_8-unit. The members of the urushiol series (XIV) (from *Rhus* spp.), glutarenghol (XV) (from *Gluta renghas*) and laccol (XVI) (from *Rhus* spp.) are derivatives of catechol with long chains in the 3-position. It has been shown in the lichen acid series that a hydroxyl is frequently found in the same place as an aldehyde. A similar feature could be expected in the 6-methylsalicylic series also and hence these catechols could be considered to arise from the corresponding salicylaldehyde derivatives (XVII) by an oxidation process involving peroxide.

B. Compounds Derived by Ring Fission

All the above-mentioned compounds arise by modifications of the C_8-unit in which the benzene ring is in tact and the original skeleton could be fairly easily discerned by inspection. Ring fission seems to be involved in a number of mould products ; hence in these cases the relationship to the original C_8-unit is not so obvious and has to be understood by careful scrutiny and analysis of the structures.

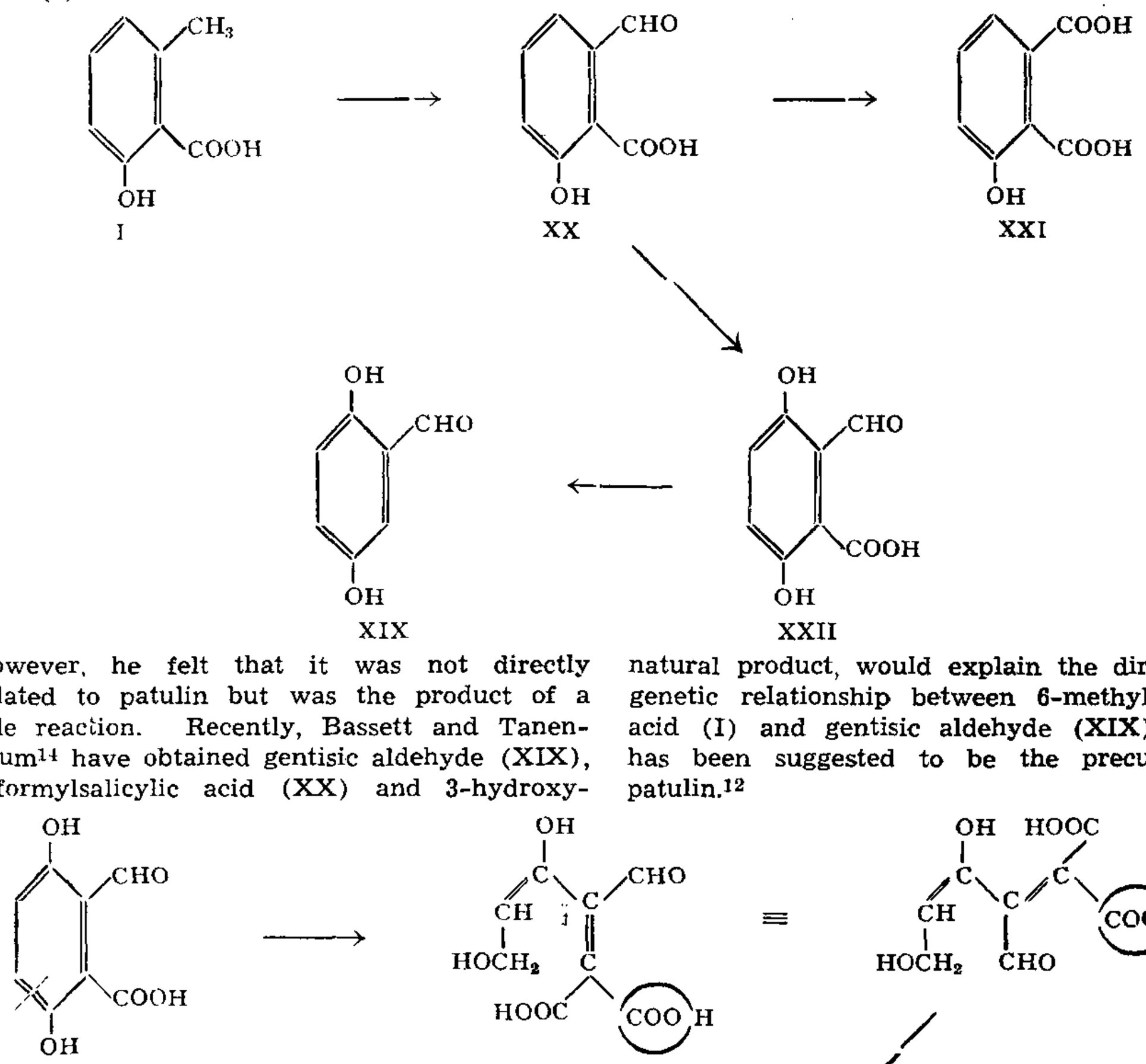
Patulin (XVIII) is an antibiotic substance of comparatively small dimensions and its constitution was finally established by Woodward and Singh.[11] Based on the co-occurrence of gentisyl alcohol, gentisic acid and patulin in the metabolic products of *Penicillium patulum*, Birkinshaw[12] suggested that gentisic aldehyde (XIX) was the precursor of patulin (XVIII). The stages involved are oxidative ring opening and



XIX XVIII

subsequent ring closure of the lactone and hemiacetal rings.

Later, Ehrensvärd[13] isolated 6-methylsalicylic acid (I) as a metabolic product of *P. patulum*. However, he felt that it was not directly related to patulin but was the product of a side reaction. Recently, Bassett and Tanenbaum[14] have obtained gentisic aldehyde (XIX), 6-formylsalicylic acid (XX) and 3-hydroxyphthalic acid (XXI) as additional products from *P. patulum* besides the earlier reported substances. They suggested that the intermediate (XXII), though not so far isolated as a natural product, would explain the direct biogenetic relationship between 6-methylsalicylic acid (I) and gentisic aldehyde (XIX) which has been suggested to be the precursor of patulin.[12]



I XX XXI XIX XXII

XXII XVIII

The above suggestion is supported by the work of Bu'Lock and Ryan[15] who used labelled 6-methylsalicylic acid[16] as a nutrient of *P. patulum* and isolated labelled patulin with the activity in the expected positions according to the above scheme of biogenesis. However, it is possible that patulin (XVIII) could be derived from the intermediate (XXII) itself as follows instead of passing through the gentisic aldehyde (XIX) as a further intermediate; the decarboxylation may take place at an undetermined stage.

SUMMARY

Members of the anacardic acid series and the accompanying orcinol derivatives are derived from orsellinic acids (C_8-compounds) with lengthened side chains. *m*-Cresol derivatives are related to the anacardic acid series by a stage of decarboxylation and quinol derivatives by an extra stage of nuclear oxidation. Hydration of *m*-cresols also seems to be possible. Catechol derivatives with long side chains are derived from the corresponding aldehydes involving a stage of oxidation. Patulin is a typical example of a product obtained by ring fission from 6-methylsalicylic acid.

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* The following are recent additions to natural benzoquinones and related compounds: (*i*) solanachromene (Rowland, R. L., *J. Amer. Chem. Soc.*, 1958, **80,** 6130); (*ii*) the corresponding plant quinone (Kofler, M., *et al.*, *Helv. Chim. Acta*, 1959, **42,** 1283; Trenner, N. R., *et al.*, *J. Amer. Chem. Soc.*, 1959, **81,** 2026) and (*iii*) ubichromenol (Leidman, D. L., *et al.*, *Chem. and Ind.*, 1959, 1019).

NOBEL PRIZE IN MEDICINE

DR. SEVERO OCHOA and Dr. Kornberg, both of the United States, have been awarded the Nobel Prize in Medicine for 1959, for their discoveries of the mechanism in the biological synthesis of the Ribonucleic Acid and Deoxyribonucleic Acid.

The nucleic acids are present both in the nuclei and in the protoplasm of living cells and they are intimately connected with cell division, mutation and the manufacture of enzymes. The ribonucleic acid (RNA) takes part in the production of proteins whereas the deoxyribonucleic acid (DNA) is present in the chromosomes as carrier of the hereditary qualities.

Dr. Ochoa was born in Luarca, Spain, in 1905 and qualified at Madrid University. In 1937 he worked in the Marine Biological Institute at Plymouth, England, and later was Nuffield Research Assistant in Biochemistry at the Oxford University Medical School. He came to the United States in 1940, and has been Professor of Biochemistry since 1954, at the New York College of Medicine. He has written a number of works on the biochemistry of muscles and of the brain.

Dr. Kornberg was born in 1918 in Brooklyn, New York, and received his M.D. at Rochester University. Until 1952 he was attached to the National Institute of Health, and later was Professor of Microbiology at the University of Washington. He is now Professor of Biochemistry at Stanford University, California.