BIOGENESIS OF NATURALLY OCCURRING TETRONIC ACID DERIVATIVES

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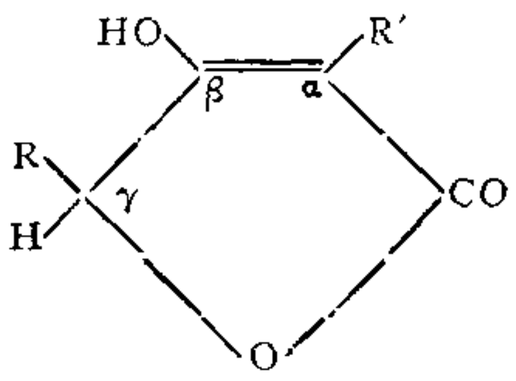
DERIVATIVES of tetronic acid (I) have been recognised as metabolic products of moulds belonging to the groups of *Penicillia* and *Aspergilli*. A number of them have been isolated by Raistrick[1] and his collaborators and their structures established and a few of them confirmed by synthesis. They are tabulated in Table I.

TABLE I

Compound		Sources
γ-Methyltetronic acid[2] (II)	..	*Penicillium charlesii*
Carlic acid[3,4] (III)	..	do.
Carolinic acid[3,4] (IV)	..	do.
Carlosic acid[3] (V)	..	do.
Carlic acid[4,5] (VI)	..	do.
Terrestric acid[6] (VII)	..	*P. terrestre*
Dehydrocarolic acid[7] (VIII)	..	*P. cinerascens*
Penicillic acid[8-10] (IX)	..	*P. puberulum*, *P. cyclopium*, *P. thomii*, *P. suavolens*, *Aspergillus ochraceus*
L-(+) Ascorbic acid[11] (X)	..	*A. niger*



I, R = R′ = H

II, R = CH_3; R′ = H

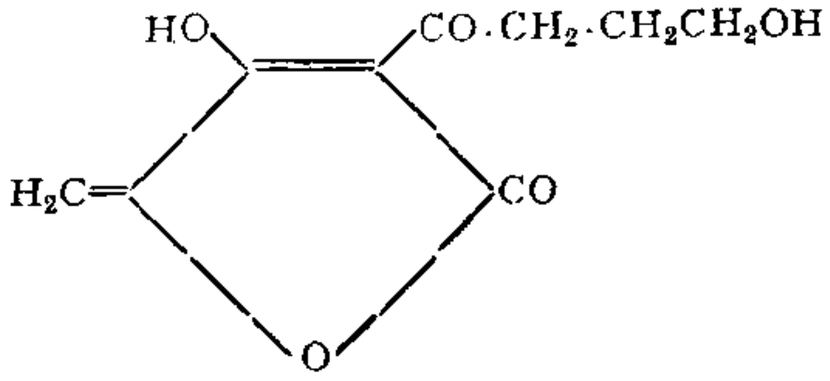
III, R = CH_3; R′ = $CO \cdot CH_2 \cdot CH_2 \cdot CH_2OH$

IV, R = CH_3; R′ = $CO \cdot CH_2 \cdot CH_2COOH$

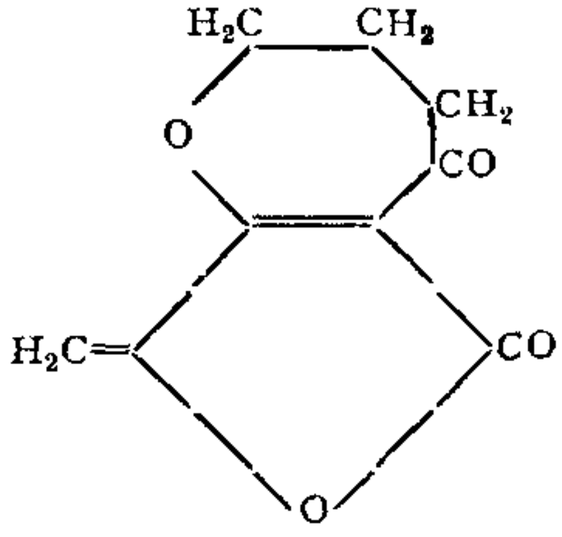
V, R = $CH_2 \cdot COOH$; R′ = $CO \cdot CH_2 \cdot CH_2 \cdot CH_3$

VI, R = $CH_2 \cdot COOH$; R′ = $CO \cdot CH_2 \cdot CH_2 \cdot CH_2OH$

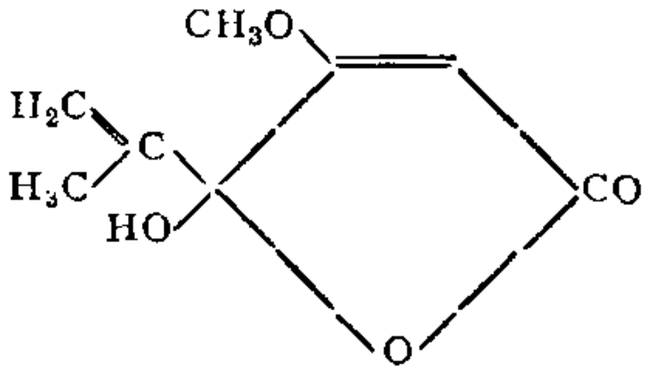
VII, R = CH_3; R′ = $CO \cdot CH_2 \cdot CH_2 \cdot CHOH \cdot C_2H_5$



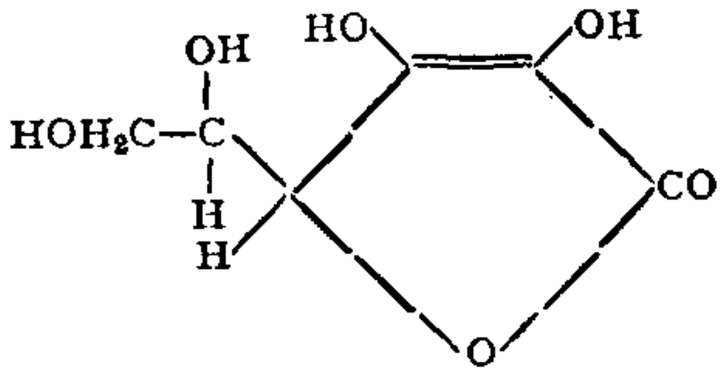
VIII



VIII *a*



IX

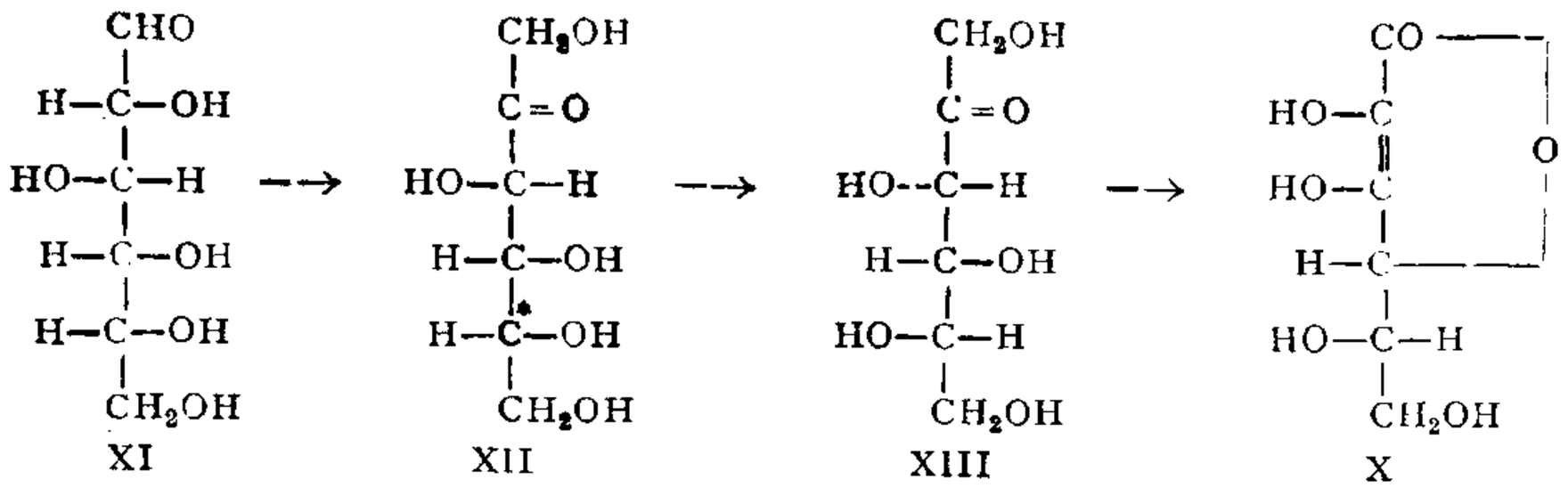


X

For the sake of convenience, compounds III, VI, VII, and VIII are here represented in the hydrated form with only one ring, though they are known to occur only in the anhydrous form having a second ring involving the acidic hydroxyl group in the β-position and that present in the side chain, *e.g.*, VIII *a* for compound VIII. Of these, the first seven compounds (II to VIII) form a closely related group and the other two appear to have different origin.

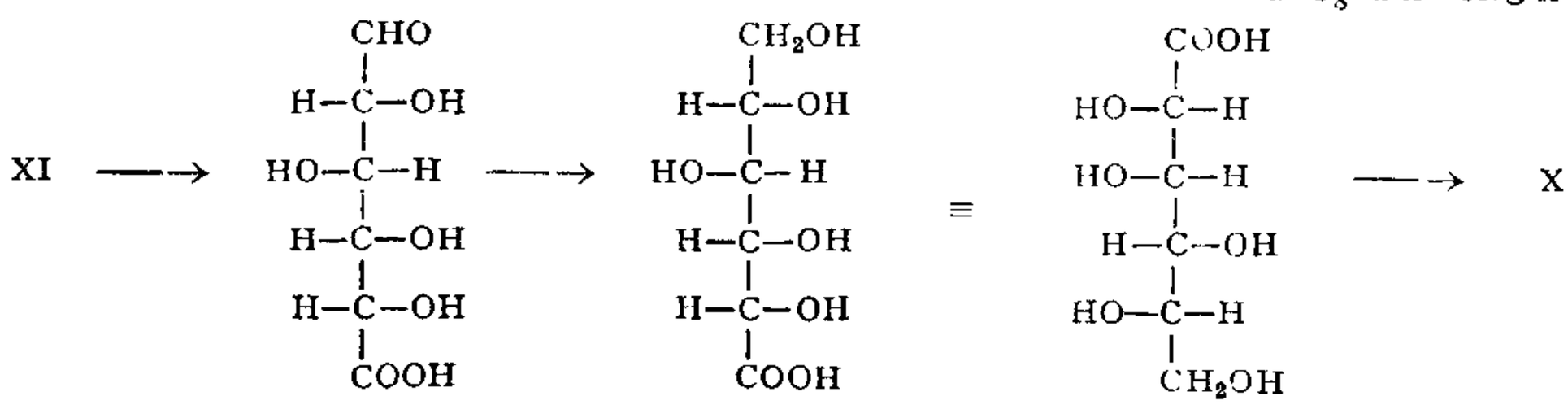
ASCORBIC ACID

L-(+) Ascorbic acid (X) (vitamin C) has been known to be widely occurring as a product of higher plants also. Its structure (X) is closely related to hexoses and hence it may have a direct biogenetic relation to carbohydrates. Suggestion was made by Rangaswami and Seshadri[12] that the biogenesis of L-ascorbic acid (X) from D-glucose (XI) may involve the following changes. D-glucose (XI) was considered to undergo easy conversion into D-fructose (XII) which, by epimerization at C_5, may lead to L-sorbose (XIII) ; the subsequent



steps were analogous to those well known in laboratory synthesis.

Horowitz *et al.*[13] found that the radioactivity (C^{14}) of the aldehyde carbon atom of D-glucose (XI) was noted in the sixth carbon atom of L-ascorbic acid (X). Based on this, Isherwood *et al.*[14] suggested that D-glucose (XI) undergoes oxidation to D-glucuronic acid (XIV) which, by reduction, forms L-gulonic acid (XV), subsequently oxidised to L-ascorbic acid (X).



However, recently Loewus and Jang[15,16] proved that the observation of Horowitz *et al.*[13] was wrong and found that the pathway of D-glucose (XI) to L-ascorbic acid (X) proceeded without cleavage and that the aldehydic carbon atom (C^{14}) of D-glucose formed the carboxyl carbon of L-ascorbic acid. In the light of these findings, the original suggestion of Rangaswami and Seshadri[12] may appear to be more valid.

Penicillic Acid

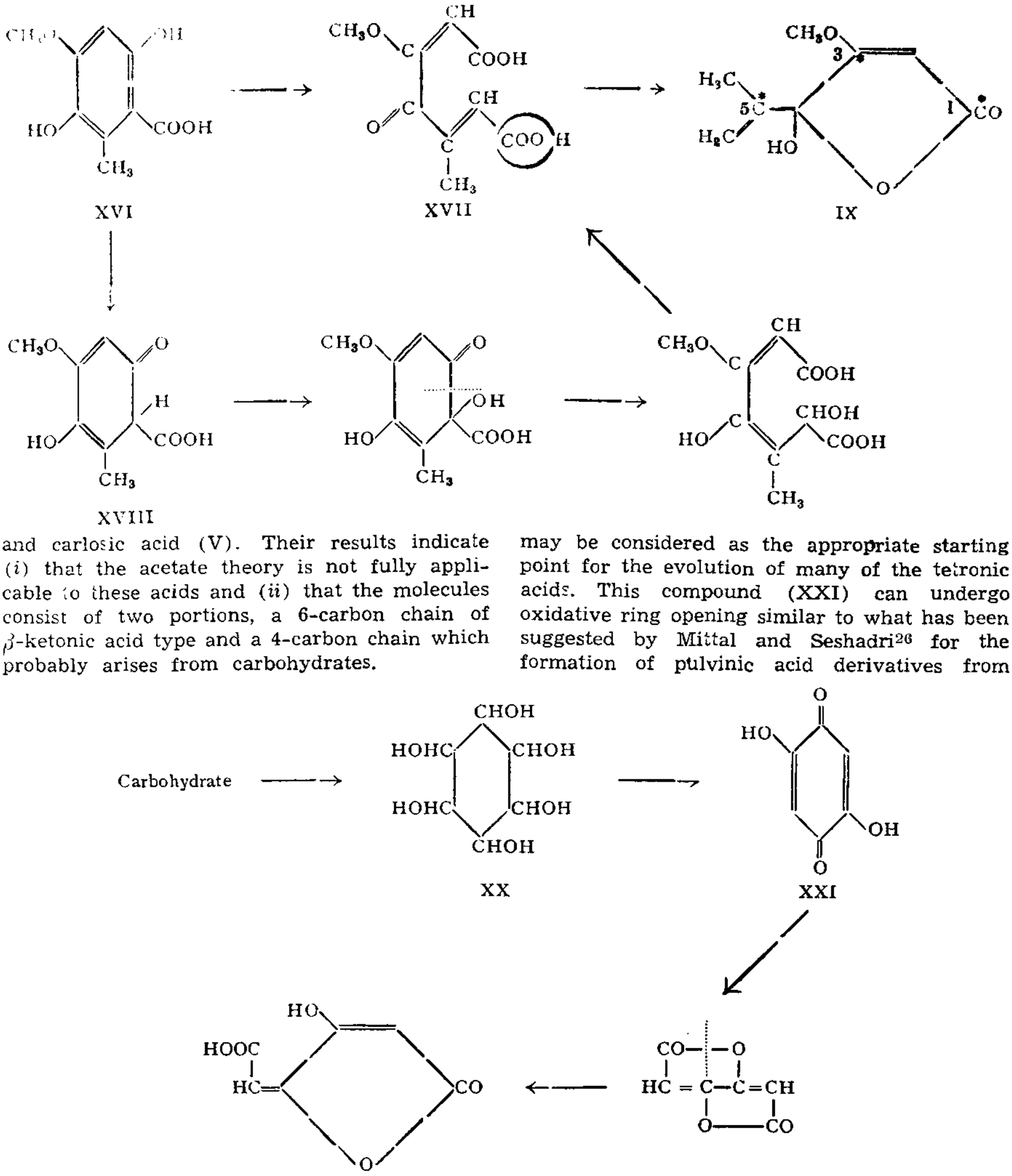
Birch and his co-workers[17] studied the biosynthesis of penicillic acid (IX). They first considered that it had a terpene origin but tracer studies with mevalonic acid lactone did not support this. However, labelled acetic acid ($CH_3.C^{14}OOH$) was incorporated in the biosynthetic penicillic acid and the activity was noted in carbon atoms 1, 3 and 5. In order to explain this, they suggested 5-hydroxyeverninic acid (XVI) as the precursor of penicillic acid (IX). Compound (XVI) was considered to undergo oxidative ring fission to (XVII) which on subsequent ring closure as well as decarboxylation would give penicillic acid (IX). This scheme is chemically acceptable. As a probable mechanism for this type of ring fission, it is now suggested that it involves α-hydroxylation of the ketonic form (XVIII) of 5-hydroxyeverninic acid (XVI) followed by hydrolysis. It is known that reagents like Fenton's, which are analogous to enzyme systems, can bring about such α-hydroxylations.[18] Ring fission of aromatic compounds in the evolution of natural products seems to be fairly common (*e.g.*, patulin[19]).

The above-mentioned C_8-unit origin of penicillic acid receives support from the fact that the concerned moulds, *Penicillium puberulum* and *P. cyclopium* are also known to produce compounds like puberulic and puberulonic acids[20] (tropolone derivatives) as well as cyclopolic and cyclopaldic acids[21] (benzenoid derivatives) respectively which are all derived from C_8-units.[22,23]

γ-Methyltetronic Acid Group

As mentioned earlier, the first seven members (*see* Table I) form a related group. Among them, the simplest would be γ-methyltetronic acid (II) and the others would arise by a further stage of substitution in the reactive α-position. The occurrence of dehydrocarolic acid (VIII) which has a methylene group in the γ-position would suggest that the common intermediate could be the carboxymethylene derivative (XIX) from which all other members may arise by feasible transformations.

The C_8-unit (orsellinic unit) appears to be unsuitable as a precursor for these tetronic acids. Similarly it is difficult to derive them directly from carbohydrates. In this connection should be mentioned the recent work of Lybing and Reio[24] on the biosynthesis of carolic acid (III)

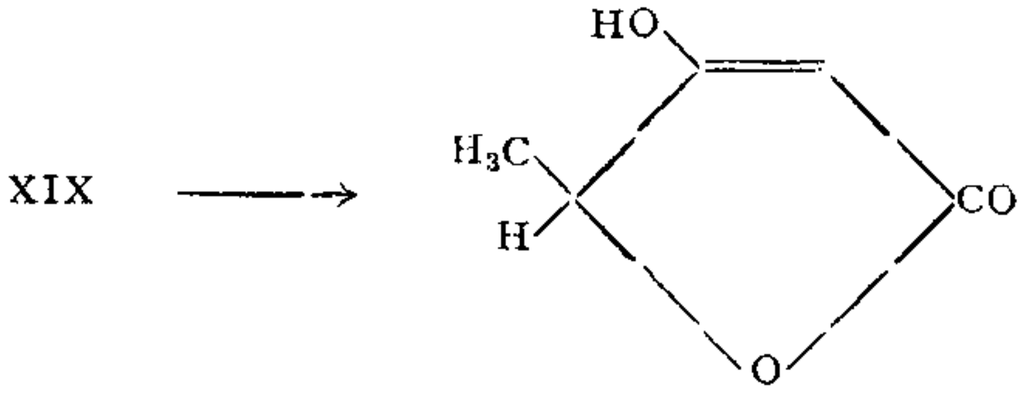


and carlosic acid (V). Their results indicate (*i*) that the acetate theory is not fully applicable to these acids and (*ii*) that the molecules consist of two portions, a 6-carbon chain of β-ketonic acid type and a 4-carbon chain which probably arises from carbohydrates.

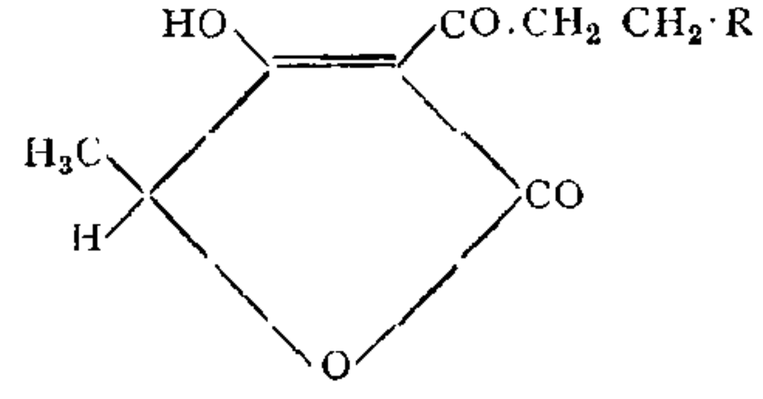
may be considered as the appropriate starting point for the evolution of many of the tetronic acids. This compound (XXI) can undergo oxidative ring opening similar to what has been suggested by Mittal and Seshadri[26] for the formation of pulvinic acid derivatives from polyporic acid series. Laboratory analogies for this type of ring fission are known. For example, polyporic acid is oxidised to pulvinic lactone by lead tetra-acetate.[27] As mentioned earlier, γ-carboxymethylenetetronic acid (XIX), which can arise from the above ring fission, may be the common intermediate.

Based on the above considerations, the following suggestion that they have their origin in hydroxybenzoquinones is now made. In an earlier paper in this series,[25] it has been pointed out that inositol (XX) is most probably the precursor for the simpler hydroxybenzoquinone derivatives. 2 : 5-Dihydroxybenzoquinone (XXI)

γ-Methyltetronic acid (II) can be formed from (XIX) by stages involving decarboxylation and reduction of the exocyclic double bond. Carolic acid (III), carolinic acid (IV) and terrestric acid (VII) have side-chains in the α-position of the above γ-methyltetronic acid (II) unit. It is easy to conceive that they arise by substitution in the reactive α-position.



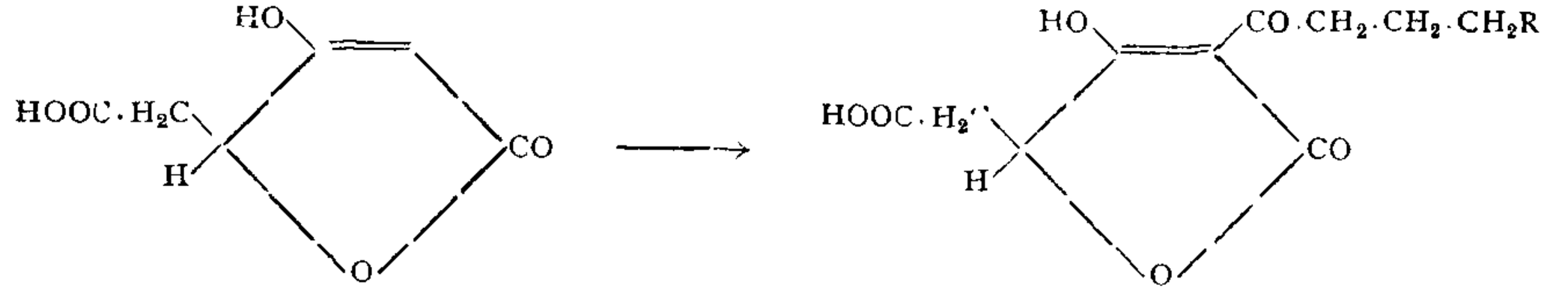
II



III, R = CH_2OH
IV, R = COOH
VII, R = $CHOH \cdot C_2H_5$

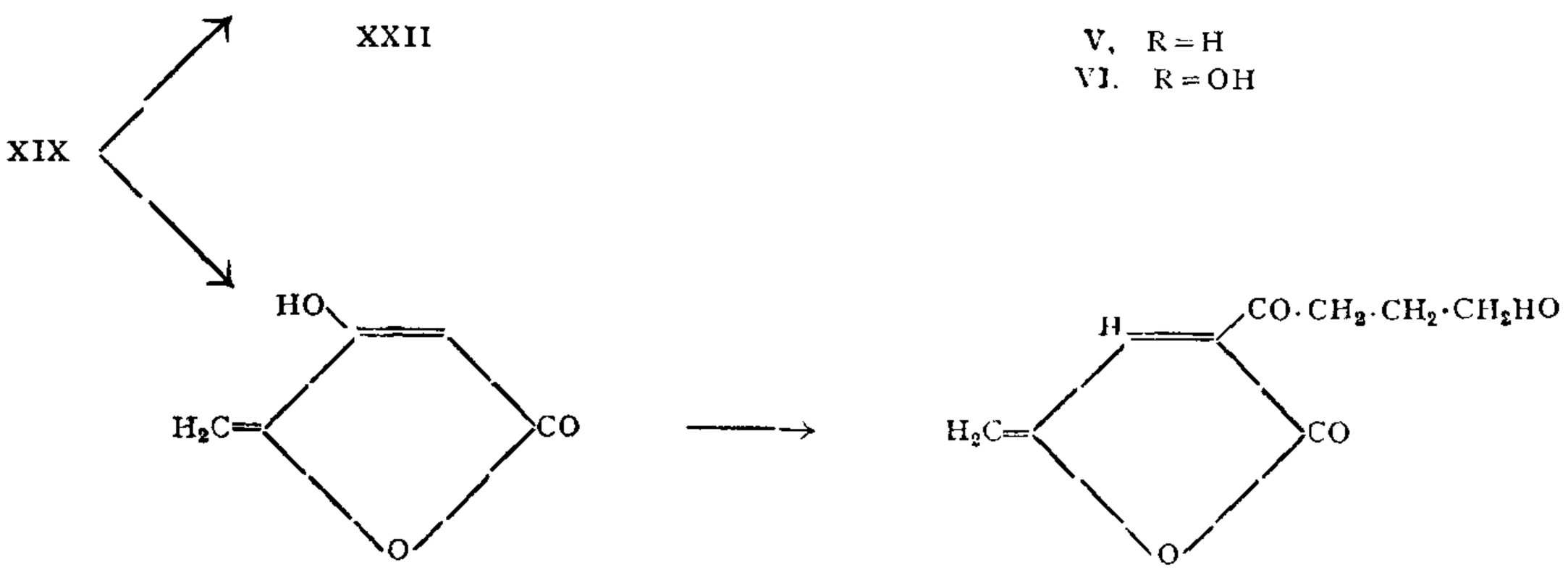
In the case of compounds (III) and (IV), a 4-carbon unit (*e.g.*, tetrose) is involved and in (VII), it is a 6-carbon unit (*e.g.*, hexose). Subsequent oxidation reduction in the side-chain would lead to the required modifications (III, IV and VII).

A similar course could be suggested for the evolution of carlosic acid (V) and carlic acid (VI). For these, the appropriate earlier stage would be the intermediate γ-carboxymethylteronic acid (XXII) which can arise from γ-carboxymethylenetetronic acid (XIX) by reduction without decarboxylation. Subsequent α-substitution by a 4-carbon unit would give carlosic acid (V) and carlic acid (VI). Dehydrocarolic acid (VIII) would require a slightly different intermediate (XXIII) which is the product of decarboxylation of (XIX) without reduction. This is followed by α-substitution by a 4-carbon chain.



XXII

V, R = H
VI, R = OH



XXIII

VIII

Summary

Tetronic acids so far known as mould products seem to fall into three categories: (1) Ascorbic acid type arising directly from sugars; (2) penicillic acid type arising from C_5-(orsellinic) unit and (3) γ-methyltetronic acid type derived from dihydroxybenzoquinone and eventually from inositol.

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NEW LIGHT ON THE PINEAL GLAND

THE Pineal gland, the seventeenth-century philosophers' 'seat of the soul', long believed to have no biological function, is now thought to have important secretory functions. Recent investigations show that there are four neuro-humoral substances in bovine pineal gland; serotonin, (5 H, 5 hydroxytryptamine), norepinephrine, histamine and acetylcholine. A fifth pineal hormone, melatonin, very recently isolated, is an antagonist of the pituitary's melanocyte-stimulating hormone and is biologically active as a skin lightening agent. These findings appear to refute the belief in the pineal's lack of function. It also has all the morphological attributes of a secretory gland, having a rich vascular and neural network. It contains as much serotonin and histamine as other parts of the brain, and half its acetylcholine level. It also contains the enzymes required for both synthesis and destruction of serotonin and related amines, and it picks up more P^{32} than any other tissues, whilst its I^{131} uptake is second only to the thyroid itself. A new adrenotrophic hormone has been isolated and identified as glomerulotrophin (GTH), probably a lipid since it is soluble in the fat solvent hexane. It is suggested that the pineal gland represents an atrophied immature pituitary which in primitive life controlled homeostasis.

BOMBAY UNIVERSITY DEPARTMENT OF CHEMICAL TECHNOLOGY

THE University of Bombay will be celebrating shortly the Silver Jubilee of its Department of Chemical Technology. The Prime Minister, Shri Jawaharlal Nehru, is expected to inaugurate the celebrations on January 3, 1960.

The Department was started in 1934 for the admission of 20 students to a two-year degree course for the B.Sc. Tech. in Textile Chemistry and Chemical Engineering following the degree of B.Sc. in Chemistry. The late Dr. R. B. Forster of Leeds University was the first Head of the Department. Under the leadership of Professor K. Venkataraman, who was Director during 1938-57, further courses were added in 1943 in the Technology of Pharmaceuticals and Fine Chemicals; Food Technology (initially Chemistry of Foods and Drugs); Technology of Intermediates and Dyes; Technology of Oils, Fats and Waxes; and Technology of Plastics, Paints and Varnishes—later changed into two separate courses: Technology of Plastics and Technology of Pigments, Paints and Varnishes. A four-year course in Chemical Engineering for the degree of B.Chem.Eng. which replaced the B.Sc. (Tech.) course was instituted in 1951. A three-year course in Pharmacy for the degree of B.Pharm. was instituted in 1958. In addition to its normal academic functions of teaching and research, the Department helps industries by carrying out research and analyses on their behalf.

The Department has, since its inception, made commendable progress. The total number of students has risen from 20 in 1934 to over 500 in 1959 and the teaching staff from 6 to 37. Over 1,500 students have so far graduated in Technology and some 300 students have received research degrees.