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SURVEY OF SCIENTIFIC WORK*)

Eschenmoser's scientific oeuvre comprises experimental and theoretical contributions to the mechanism and stereochemistry of organo-chemical and biochemical reactions, to the concept and mechanistic elements of the "biogenetic isoprene rule", and to problems related to chemical bonding and structure. One of the main themes of his research was the development of new reactions and methods for chemical synthesis in the context of the total synthesis of natural products. His work in the latter field culminated in the total synthesis of vitamin B_{12} and the development of a comprehensive synthetic chemistry of corrinoids and corphinoids relating to the chemical synthesis, biosynthesis, and etiology of the vitamin B_{12} structure. Most recent experimental and theoretical investigations aim at an etiology of nucleic acid structure in the wider context of a search for the chemistry of life's origin.

In his doctoral thesis (1951), Eschenmoser made proposals on the mechanism of **cationic polyene cyclization** in the terpene series and postulated that the constitutional formulae of all sesquiterpenes known at the time are derivable from the formula of a common acyclic sesquiterpene precursor via cationic cyclization and rearrangement pathways. On the basis of this postulate, he proposed new constitutional formulae for the sesquiterpenes zingiberene, β-caryophyllene, α-caryophyllene (humulene), cedrene, elemol and lanceol. He then extended the concept to a detailed mechanistic derivation of the constitutional formulae of all tetra- and pentacyclic triterpenes known at the time from the acyclic triterpene hydrocarbon squalene, proposing the principle of oxidative initiation of the biological cyclization of this common precursor to cyclic triterpenes and steroids. These contributions constituted the conceptual and mechanistic basis for the announcement of the **biogenetic isoprene rule** by L. Ruzicka, A. Eschenmoser and H. Heusser in 1953. Subsequent experimental studies at ETH on model polyene cyclizations established rules that govern the stereochemical course of these reactions, including the potential stereochemical consequences of the conformational chair/boat-dichotomy of cyclizing polyene chains. In 1955, Eschenmoser and D. Arigoni, jointly with L. Ruzicka and O. Jeger, proposed a complete **stereochemical interpretation of the biogenetic isoprene** rule for all tetra- and pentacyclic triterpenes then known.

Contributions to the field of **mechanism and stereochemistry of organic reactions** beyond those on cationic polyene cyclizations include: the identification of strain release as the dominating factor responsible for the higher reaction rates of axial, as compared to equatorial epimers in oxidations of secondary alicyclic alcohols with chromic acid (1955), the concept and experimental demonstration of the non-occurrence of endocyclic SN_2-type reactions at saturated carbon, corroborating the principle of a near-to-colinear arrangement of incoming nucleophile, leaving group and substitution center in the transition state of SN_2-reactions (1970), and an extended study on the stereochemistry of allylic reactions, testing the potential of the qualitative bent-bond model of multiple bonds to predict the stereochemical course of such reactions (1978, 1987, 1989). The work on the structure of SN_2-transition states defined the stereoelectronically relevant dichotomy of the endo- versus exo-cyclic nature of nucleophilic substitution reactions and anticipated extensive follow-up studies by other authors ("Baldwin rules").

Investigations relating to questions of **chemical bonding and structure** include: the synthesis (in the context of the synthesis of colchicin) and theoretical studies (together with E. Heilbronner) of benzotropylium cations (1957), studies on the constitutional factors that determine slow inversion of pyramidal nitrogen exemplified by the isolation at room temperature of diastereomeric forms of an N-chloro-aziridine and of an N-methoxy-1,2-oxazolidine containing a trivalent nitrogen as a stereogenic center (1969), and the structural studies on enamines in the context of investigations on the mechanism of enantioselection in aldolization reactions catalyzed by proline (with J. D. Dunitz, 1978, 1980).

Most of Eschenmoser's contributions to the field of **new reactions and methods for chemical syntheses** derived from his involvement in natural product synthesis. An early synthetic problem in the monoterpene field led to the mechanistic concept of anionic C,C-bond fragmentation reactions and the recognition and exemplification of their potential for the regiospecific formation of olefinic double bonds (1952), a reaction type that was later extensively studied and propounded by others ("Grob Fragmentation"). Further contributions to fragmentation chemistry were the base-catalyzed cleavage of 1,5-dicarbonyl compounds (1953), the concept and experimental demonstration of α,β-epoxyketon-alkynone fragmentations (1967, 1968, 1972), and the use of decarboxylative tandem-fragmentations in regio- and stereoselective approaches to unsaturated macrolides (1979). Synthetic methods developed at ETH in the context of the corrin and vitamin B_{12} project include: a reductive C,C-bond fragmentation (1964), the amide acetal version of the Claisen rearrangement (1964, 1969, 1979), the C,C-bond formation by enamine-iminoester condensation (1964) and a variant of it dubbed "sulfide contraction" via oxidative and alkylative coupling (1969, 1973). The last mentioned methods provide a general access to corrinoid chromophores and, besides the formation of vinylogous amidines, the synthesis of vinylogous amides and 1,3-dicarbonyl systems (1971). The quest for methods for the C-methylation of the corrin chromophore - in conjunction with questions that arose in the context of the work on SN_2 substitution and

nitrogen inversion - led to the preparation, via an unforeseen fragmentation process, of methylidene-dimethyl-iminium iodide, a useful Mannich-reagent in crystalline form (1971).

Further contributions to synthetic methodology include: The use of amide acetals for alkylative esterification of sterically hindered carboxylic acids (1965), the halolytic cleavage of sterically hindered methyl esters by lithium iodide (1960), intramolecular C-alkylations at β- and δ-positions in oximes of conjugated enones and dienones (1958, 1965) as early examples of the type of reactivity-site inversion later known as "Umpolung", and a comprehensive study of electrophilic cycloaddition and substitution reactions on isolated olefinic bonds involving N-vinyl-nitrosonium ions derived from α-chloro-nitrones (1972, 1973). Such a vinyl-nitrosonium ion gained prominence in the final phase of the B_{12} project as reagent for the selective hydrolysis of a primary amide group to a carboxyl group in the presence of reactive methylester groups.

Eschenmoser's activity in the field of **natural products synthesis** was focussed on two major targets, each of them representing a central problem, in its time, in the field of total synthesis: the alkaloid **colchicin** in the second half of the fifties, and **vitamin B_{12}** in the sixties. The synthesis of colchicin (1959) was followed by the first synthesis of a corrin (1964), an accomplishment that paved the way towards the chemical synthesis of vitamin B_{12}. This goal was achieved in 1972 in close collaboration (since 1965) with the research group of R. B. Woodward at Harvard, resulting in two different, yet chemically interrelated and concomitantly completed, syntheses of cobyric acid, amounting to two different (at the time, formal) total syntheses of vitamin B_{12}. In the joint Harvard-ETH variant, the ligand system of the vitamin was constructed by connecting the stereochemically complex "Harvard component" (containing rings A and D) with an "ETH component" (containing rings B and C) by sulfide contraction via alkylative coupling, followed by the macrocyclization step between rings A and B by thioiminoester-enamine condensation or, alternatively, sulfide contraction. The ETH variant of the synthesis (1969-1972, 1974, 1977) started with the same "ETH-component", proceeded by attaching rings A and D via sulfide contraction to give an A/D-secocorrinoid cadmium (II) complex which - initiated by an unprecedented photochemically induced (1,16)-sigmatropic hydrogen shift - underwent a final macrocyclization between rings A and D to afford the 15-membered corrin ring with high diastereoselectivity. In both cobyric acid syntheses, the overall strategy and the chemistry of chromophor construction closely followed the patterns established at ETH in three model syntheses of corrin complexes published in 1964, 1967 and 1969.

Following the synthesis of vitamin B_{12}, Eschenmoser's research shifted in the direction of a **synthetic chemistry of hydro-porphinoids** related to the problem of vitamin B_{12} biosynthesis and, in turn, to the quest for a **chemical etiology of the vitamin B_{12} structure.** In a systematic search for non-photochemical variants of the (A/D)-macrocyclization process, a whole range of (A/D) ring closure

reactions (reductive, oxido-reductive, decarboxylative, tautomerizative, and ring-contractive variants) of corrin ring formations was discovered (1975-1981). A new hexahydro-porphinoid ligand system, named "corphin", was made and shown to represent, as metal complex, a thermodynamic sink in the landscape of hexahydro-porphinoids (1980-1986). Suitably substituted hydro-corphinoid complexes of nickel(II) and cobalt(III) were shown to undergo ring contraction to corresponding corrin complexes. Hepta-cyanomethl-cobyrinate, a cobyrinic acid derivative devoid of the vitamin's nucleotide loop and containing seven carboxyl functions in undifferentiated form as mildly activated cyano-methyl ester groups, was shown to produce selectively vitamin B_{12} when allowed to react with the free nucleotide chain (followed by ammonolysis). This finding demonstrated that the specific site of the nucleotide loop attachment to the vitamin's ligand system is both kinetically and thermodynamically the favored site among all possible other sites (1988). The overall results of these investigations revealed an underlying generational simplicity of the outwardly complex vitamin B_{12} molecule, a feature thought to be relevant to the etiology of biomolecules with a corrinoid structure (1988).

In the context of the investigations on the chemistry of corphinoid ligand systems it was shown, jointly with A. Pfaltz and B. Jaun at ETH and in collaboration with the microbiologist R. Thauer in Marburg, that the Factor F430, a coenzyme from methanogenic bacteria, has a hydro-corphinoid structure (1982-1985). The elucidation of the chemical constitution of this cofactor was complemented by the synthesis of nickel(II) model complexes containing the cofactor's novel chromophor system (1984).

The work on the etiology of the vitamin B_{12} structure provided the inspiration to become engaged in systematic experimental studies relating to the broader challenge of a search for the chemistry of life's origin (1987). The main part of these studies was focusing on the synthesis, structure, and properties of potentially natural nucleic acid alternatives, aiming at an understanding of the structural and functional criteria that may have determined Nature's choice of RNA and DNA as genetic systems (**chemical etiology of nucleic acid structure**). This work, carried out since 1987 at ETH and since 1996 at Scripps together with R. Krishnamurthy, established that the capability of Watson-Crick base-pairing is widespread among potentially natural nucleic acid alternatives taken from RNA's structural neighborhood, that Nature did not select RNA as genetic system based on the criterion of maximization of base-pairing strength, and that hexopyranose analogs of RNA derived from allose, altrose and glucose could not have been evolutionary competitors of RNA since they lack the capability of informational Watson-Crick base-pairing (1993, 1999, 2007). It was furthermore shown that Watson-Crick pairing can mediate different "base-pairing languages" in the sense that complementary base sequences of a given type of backbone may pair with each other, but not with sequences of pairing systems that have sufficiently different backbones. Most recently, the work has been extended to oligomer systems containing oligo-dipeptide backbones tagged with alternative recognition elements such as triazines and 5-amino-

pyrimidines. It was found that a correlation exists between the ΔpKa value of a pair of recognition elements and the relative pairing strength of that pair, suggesting that the canonical Watson-Crick base-pairs may represent a functional optimum with regard to informational pairing in aqueous medium (2007).

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