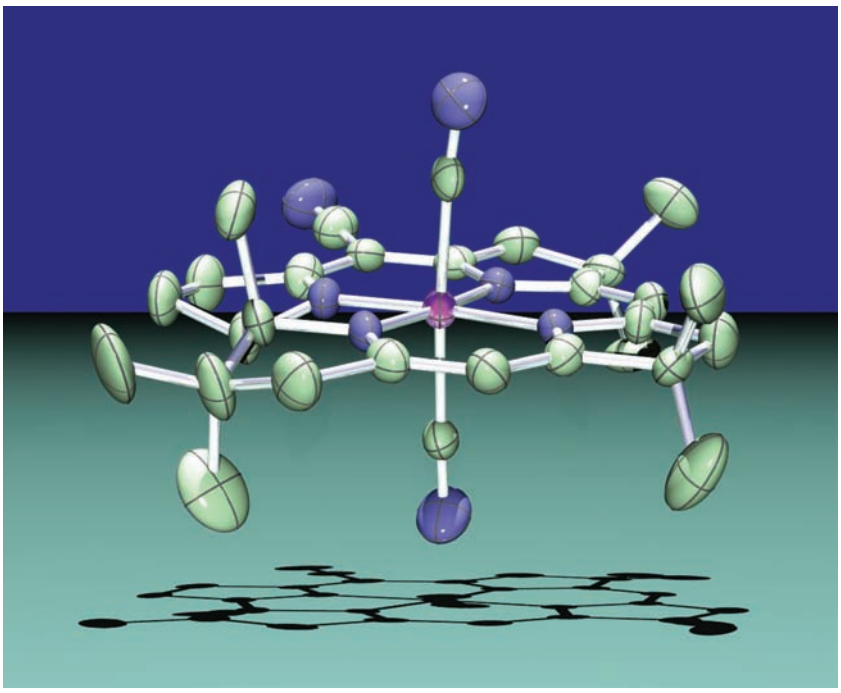
Corrin Syntheses

by

Albert Eschenmoser



Ray-tracing illustration by *Christian Lehmann* (ETH Lausanne)
of Dicyanocobalt(III)-15-cyano-1,2,2,7,7,12,12-heptamethylcorrinate;
X-ray structure by *P. Galen Lenhert* and *T. J. Shaffner*
(Thesis, Vanderbilt University, 1969)

(Photo: *Martin Friedlander*)

Albert and ***Elisabeth Eschenmoser***

This issue of *Helvetica Chimica Acta* is dedicated to ***Albert Eschenmoser*** (whom to introduce to the readers would be 'carrying coals to Newcastle'!) and his art of Organic Synthesis.

I feel highly privileged and deeply honored that he trusted me to meet the challenge of '*resurrecting his corpses in the cellar*', *i.e.*, to edit and publish '*a series of manuscripts, entitled* '*Corrin Syntheses – Part I–VI*", which had been originally planned to be submitted to *Helvetica Chimica Acta* around 1975, but remained unfortunately unpublished. These syntheses (according to the opinion of the editor) reveal 'Organic Synthesis' as '*Art*', more specifically, as '*Sculpture*', representing at the same time one of the most remarkable accomplishments in Organic Chemistry.

May they serve as '*guides*' and '*guidance*' for present and future generations of chemists…

M. Volkan Kısakürek

Introductory Remarks on the Publication Series 'Corrin Syntheses – Parts I – VI'

by **Albert Eschenmoser**

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Between 1960 and 1980, an extensive series of preliminary communications and lectures was published on work carried out by my research group at the ETH in the context of the chemical synthesis of vitamin B_{12} (*cf.* [1 – 42] in *Part I*). These communications reported on two model syntheses of the corrin ligand system, published in 1964 and in 1969, as well as on the ETH part of the collaborative effort of my group and that of *R. B. Woodward* at Harvard on the B_{12} project. Two variants of the chemical synthesis of vitamin B_{12} were concomitantly achieved in 1972, the one *via* $A \rightarrow B$ corrin ring closure, pursued collaboratively in both laboratories, and the photochemical variant *via* an $A \rightarrow D$ corrin ring closure, accomplished at ETH. At the heart of the latter was the light-induced *A*/*D*-secocorrin → corrin cycloisomerization, a novel reaction that had originated as a 'targeted discovery' in the last step of the second model corrin synthesis. Later communications from our laboratory described work carried out in the wake of the B_{12} project, efforts dealing with the scope and mechanism of the photochemical $A \rightarrow D$ ring closure. What followed were communications describing a search for 'biocompatible' (non-photochemical) versions of that process, work done in the context of, and parallel to, research on the biosynthesis of vitamin B_{12} going on in other laboratories at that time.

Since none of all these communications qualified as 'full paper' in the conventional sense, the details of the experimental procedures involved in these extensive studies remained unpublished. Around 1975, I started writing a series of manuscripts, entitled 'Corrin Syntheses – Parts I – VI'[1]), with the intention of covering in full detail the work carried out at the ETH from early 1960 up to the time of the writing, and publishing them, once completed, all together in the same issue of *Helvetica Chimica Acta*. The manuscripts were written in German, as were all papers the author published in this journal at that time. The series was not intended to encompass the work on the synthesis of vitamin B_{12} itself, as was explicitly stated in the introduction to *Part I:* '*Die ETH-Arbeiten zur Synthese von Vitamin B_{12} sind nicht Thema dieser Publikationsreihe, denn diese werden, gemeinsam mit den Vitamin B_{12} Arbeiten von* R. B. Woodward *und Mitarbeitern, Gegenstand einer eigenständig zu erscheinenden Veröffentlichung sein*'[2]).

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[1]) Some of the surviving notes refer to 'Parts I – VIII', pointing to a plan for a series that would have encompassed additional Parts of the work on '*Post-B_{12} Problems in Corrin Synthesis*'.

[2]) '*The work done at the ETH on the synthesis of vitamin B_{12} is not to be a part of this series, since it will be subject of a joint publication of the Harvard and the ETH groups, covering the B_{12} work done at Harvard as well as at the ETH*'. This reflects the author's personal intention at the time when he was starting to write the introduction to *Part I* (around 1975; *cf.* the note at the end of lecture abstract published in [20] of *Part I*).

Due to a variety of circumstances, neither the series of full papers on synthetic corrins, nor a joint communication of the Harvard and ETH group on the synthesis of vitamin B_{12} ever appeared in print. At the day of the untimely death of *Robert Burns Woodward*, July 8th 1979, no manuscript of a joint publication from the two laboratories existed[3]). What existed were the complete manuscripts of three full papers, '*Corrin Syntheses*', *Parts II*, *III*, and *IV*, written by the author in the period of 1975–1977, as well as the manuscript of *Part V* (without the *Exper. Part*) and, finally, about half of the manuscript of a *Part I*, intended as an introduction to, and an overview of, the whole series.

I am deeply grateful to the Editor-in-Chief of *Helvetica Chimica Acta*, *M. Volkan Kisakürek*, who, after having become informed of the existence of those '*corpses in the cellar*' in April 2011, encouraged the author to reactivate the project and to complete

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[3]) Soon after *R. B. Woodward*'s death, *Engelbert Zass*, a former post-B_{12} graduate student of mine, who worked on a topic unrelated to corrin synthesis and subsequently remained in the group as a postdoctoral assistant, agreed with me upon a plan to screen, write, and publish in one single 'full paper' the entire experimental work accomplished at Harvard and at the ETH on the synthesis of vitamin B_{12}. This would cover the A → B variant of the B_{12} synthesis collaboratively pursued in the two laboratories, as well as the photochemical A → D variant of B_{12} synthesis. Since the documentation of all the work performed at the ETH was already accessible in the *printed* ETH theses of the Ph.D. students who were involved in the B_{12} project, it was decided to tackle first the experimental work conducted at Harvard. Writing this up had to be based on 67 postdoctoral reports and supplementary material, copies of which Professor *Yoshito Kishi* had arranged to be sent from Harvard to ETH. *Engelbert* started on the task in early 1980, working on the project as a part-time activity in close contact with the author, and, until 1986, he had written up the entire experimental part of the Harvard synthesis of the A/D component, as well as the collaborative part of the A → B ring closure variant up to the stage of the 5,15-bisnor-tetramethyl-cobyrinate-c-dimethylamide-f-nitrile, the common intermediate of the two variants of the B_{12} synthesis. At this stage, the writing turned back to the work at the ETH on both the (A → B)- and the (A → D)-ring closure variant of the B_{12} synthesis, with the intention of eventually adding the description of the remaining steps between the common intermediate mentioned above and cobyric acid, steps that had been carried out in the two laboratories in strictly parallel, manner whereby Harvard used material prepared by the A → B variant, and ETH by the A → D variant. The writing-up process was interrupted in late 1986, sporadically taken up again in 1990, and came to a close in 1992. In 1993, *Engelbert* was offered a permanent position in the Department Library, and in 2003 he was elected Head of the Chemistry-Biology Information Center at the ETH.
On 12th of August 2014, *Engelbert* delivered the *Herman Skolnik* Award Address before the Division of Chemical Information at 248th ACS National Meeting, in San Francisco, where he discussed the state of the B_{12} publication project reached in 1992, at the same time indicating signs of hope that the task might eventually be realized; cf. http://www.slideshare.net/EngelbertZass1/of-a-landmark-total-synthesis-yet-unpublished-in-full-experimental-detail-vitamin-b12; W.A. Warr, *Chem. Inf. Bull.* **2014**, *66(4)*, 22–40; http://bulletin.acscinf.org/PDFs/CIB_66-4.pdf). As a genuine autodidact, *Engelbert* had grown over the years to a uniquely competent, internationally known personality in 'chemical informatics', as the laudatio of his *Skolnik* Award states: '*For outstanding contributions and achievements in the practice of chemical information science, notably for his lifelong work in education, research and development activities. Throughout his career he has been a true bridge-builder and mediator between database producers, vendors, publishers, librarians and end-users in chemistry, contributing to advancing chemical information as a whole*'. *Engelbert*'s merits had been recognized already before by the *Mike-Lynch*-Award of the CSA Chemical Structure Association Trust in the UK (2011), as well as by the *Gmelin-Beilstein*-Denkmünze of the Gesellschaft Deutscher Chemiker (2012). *Engelbert* retired from his position at the ETH in May 2012.

the series, at the same time offering support and the prospect of publishing everything, once completed, together in this journal, despite the decades that have elapsed since the work had been done. The author let himself be reactivated with enthusiasm, not the least because one of the main reasons behind his neglect to publish the work on corrins, namely, his excursion into studies on the etiology of nucleic acid structure, had come to a close in 2011 (*cf.* [76] in *Part I* of the series).

Why publish experimental details of research in synthesis after so many years? First of all, the author takes comfort in finally living up to what persisted as an unfulfilled duty over all the years. Furthermore, he enjoys returning, in a nostalgic mental journey, back to the chemical territory on which he had spent the central years of his research career. Writing about the work from today's perspective also allows him to add commentaries that may give the writing the character of the '*Corrin Chapter*' of a chemical autobiography. It may be said that 'becoming outdated' happens eventually to any publication describing experimental work in chemistry, but this may perhaps be less the case for a documentation of research that was basically directed at establishing and understanding the chemistry of molecular structures occurring in living nature. The work on the chemical synthesis of corrins and of vitamin B_{12} was intended to be such a work, besides being a contribution to the field of organic synthesis at its time. Since the chemical structure of the most complex of all vitamins had been revealed by X-ray structure analysis and *not* by chemical degradation, research on its synthesis amounted to exploring the chemistry of this extraordinary biomolecule.

Last, but perhaps not least, a chemist looking at a reaction sequence of the synthesis of a natural-product structure may sometimes feel like looking at a *sculpture* composed by molecular transformations. What can be true for the world of architecture, may also be true for the world of molecules where structures are built by target-oriented chemical syntheses: creating structures in both worlds can involve more than just techniques and may transcend the 'already seen before'. Yet, whether a given piece of such 'architecture' or 'sculpture of molecular transformations' is worth surviving in the minds of people, is up to the future to decide.

The series of six *Parts* mentioned correspond in content and organization to the original publication plan adopted in the 1970. The topics are as follows:

Corrin Syntheses – Part I:
Introduction and Overview

Corrin Syntheses – Part II:
Synthesis of Corrin Complexes via A → B *Ring Closure: Preparation of Hemicorrinoid B/C-Components, and Model Studies on Enamides and Imido-ester C,C Condensations*

Corrin Syntheses – Part III:
Synthesis of Corrin Complexes via A → B *Ring Closure: Preparation of A/D Components*

Corrin Syntheses – Part IV:
Synthesis of Corrin Complexes via A → B *Ring Closure: Coupling of A/D und B/C Components to Corrin Complexes by Imidoester/Enamine Condensations*

Corrin Syntheses – Part V:
Synthesis of Metal-free Corrin Derivatives via A → B *Ring Closure: Complexation of the Free Corrin Ligand with Metal-Ions, and Some Properties of the Corrin Ligand in Corrin Complexes*

Corrin Synthesis – Part VI:
Synthesis of Corrin Complexes via Photochemical A → D *Ring Closure: Construction of Corrinoid Chromphors Systems by the Sulfide-Contraction Method and the Photochemical A/D-Secocorrin → Corrin Cycloisomerization Reaction*

The manuscripts written in the 1970s (*Parts II – IV*, the theoretical section of *Part V*, and a fragment of *Part I*) were in German, and they are now published in essentially unchanged, only slightly re-edited form. No earlier manuscript existed for *Part VI*; it has now (2013/14) been written *ab initio* in English, the experimental part in German. The other manuscripts are presented in their original language. However, all the *Figures* and *Tables* in *Parts I – V* are accompanied by English captions, in which relevant aspects presented are outlined such that the sum of all captions of a *Part* reflects the essence of its content. Writing the experimental parts of *Parts V* and *VI* after so many decades was only possible because the experiments of the syntheses of corrins (as well as vitamin B_{12}) are extensively documented in theses of former Ph.D. students. The content of these theses, especially their experimental parts, had been carefully checked and edited by the author at the time when they were written. The theses had appeared in printed form, and today their full texts are accessible in the internet under *www.ETH e-collection* through search by the name of the theses' authors. Experiments carried out by postdoctoral collaborators were included – apart from corresponding postdoctoral reports – also in the experimental parts of thematically related theses whenever such experiments were essential for the documentation of a given topic in a thesis.

Part I of the series, written in the late 1970s up to *Sect. 2.5* of *Chapt. 2* and originally intended to be an introduction into the work on 'corrin synthesis', has now been extended to an comprehensive overview of the work on the chemistry of corrins accomplished at the ETH up to 1970s. The review puts emphasis on delineating the lines of thought and the strategies that determined the planning of projects, besides summarizing experiments and their results. In extending this *Part I*, written in the 1970s, the attempt to maintain the linguistic uniformity of the introductory communication by continuing in German was found inappropriate, and, therefore, English captions gradually became the main text.

In *Part I*, the list of references starts by chronologically enumerating the publications [1 – 42], covering all the publications of the work performed on corrins and vitamin B_{12} at the ETH 1960 up to the time of the writing in the late 1970s. This list remains unchanged in the present version of *Part I*. The post-B_{12} work at the ETH (mostly) in the 1980s is covered by references [43 – 76]. References [1 – 76] represent the complete list of publications by the author's research group in the field of corrins, vitamin B_{12}, corphins, and other hydroporphinoids, including chlorophyll derivatives and coenzyme F 430. To facilitate the use of the list, all items include the title of the

respective publication. This is also the case for the selection of Ph.D. theses, listed in references [77–132], the contents of which all refer to the topics just mentioned.

The references of *Parts II–V* have not been updated in order to maintain content and character of manuscripts written in the 1970s. However, the English captions to the *Figures* of *Parts I–V* also deal, whenever necessary, with work carried out at the ETH or elsewhere after that time. This applies especially to the recent experimental studies toward alternative syntheses of B_{12} as pursued by *Robert Stevens*, *Peter Jacobi*, and *Johann Mulzer*, and their co-workers. The captions may also contain comments that reflect changes in the perception of our own research after so many years since the work had been done.

Comments have been made on various occasions on the relationship and significance of the model studies on corrin synthesis to the project of vitamin B_{12} synthesis. Such comments are prompted by the fact that the two different strategies of corrin synthesis developed in the model studies at the ETH became the strategies for the construction of the corrin chromophor system in two chemically different, yet intricately entangled B_{12} syntheses accomplished at Harvard and at the ETH in 1972. Many of the methodological challenges and reactivity problems encountered along the path to synthetic vitamin B_{12} had been first explored in a model series; much of such interplay between model studies and the B_{12} project is recorded and discussed in the six 'Corrin' papers, especially in *Part I*. Since the variant that culminated in the photochemical *A*/*D*-secocorrin → corrin cycloisomerization played a crucial role in the final phase of that joint accomplishment, *Part I* of the series contains a chapter, the content of which deviates from the overall purpose of providing an introductory overview on corrin syntheses in that it contains a retrospective documentation of the contributions of the ETH group in the final phase of the ETH/Harvard collaboration (*Chapter 3:* '*The Final Phase of the Harvard/ETH Collaboration on the Synthesis of Vitamin* B_{12}'). This chapter is an attempt to finally establish a more balanced view on what had been accomplished by the two groups.

I am deeply indebted to a large number of Ph.D. students and postdoctoral co-workers with whom I had the privilege to collaborate in the research reported in this series of papers. Their names are listed below (in chronological order) under headings that indicate the topics to which they contributed. Quite naturally, there were collaborators who succeeded in contributing more than others; the names of those who were fortunate to do so will prominently be mentioned again in the context of their contributions described in *Parts I–VI*. Perhaps more often than not, lack of success of those who were less fortunate is to be retrospectively attributed to intrinsic weaknesses in the projects assigned to them, thus, the responsibility for failure is mine, not theirs.

Synthesis of Corrins and Corphins in the Model Series (1960–1973):

Ph.D. Students: *Ehrhard Bertele, Rolf Scheffold*† [4]*), Hanspeter Gribi, Helmut Boos*†*, Heinz Gschwend, Werner Häusermann, Ivo Felner-Caboga, Pius Wehrli*†*, Albert Fischli, Ernst-Ludwig Winnacker, Hans-Ueli Blaser, Martin Roth, Hans-Jakob Wild*†*, Peter M. Müller, Erwin Götschi, Niklaus Bühler, Bruno Hardegger, Gerd Kloster*†*, August Rüttimann*†.

Postdoctoral co-workers: *Mario Pesaro, Fritz Elsinger*†*, Arthur Peter Johnson, Dusan Miljkovic, Dieter Bormann, Yasuji Yamada, Jürgen Schossig, Larry Ellis, Brian B. Place, John Gleason.*

Synthesis of Vitamin B_{12} (1960–1973, since 1965 collaboratively with the Harvard group):

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[4]) † Deceased.

Jakob ('Schaggi') Schreiber (1921 – 1991), member of the author's research group from 1951 to 1991.

Ph.D. Students: *Jost Wild, Urs Locher*†*, Alexander Wick, Lucius Werthemann, Peter Löliger, René Wiederkehr, Willy Huber, Paul Dubs, Peter Schneider, Walter Fuhrer, Hans Maag, Walter Schilling.*

Postdoctoral co-workers: *Joseph M. Muchowski , Heinz Gschwend, Alexander Wick, Terry L. Bogard, James J. Sims, Reinhart Keese, David Coffen*†*, Bernhard T. Golding, Fritz Karrer*†*, Peter Schneider, Naoto Hashimoto, Naruyoshi Obata*†*, Andrew B. Holmes, Walter Hunkeler*†.

Post-B_{12} Work on the Chemistry of Corrinoids, Corphinoids, and other Hydroporphinoids (1973 – 1992)

Ph.D. Students: *Bernhard Kräutler , Andreas Pfaltz, Reinhard Neier, René Nordmann, Vittorio Rasetti, Christof Angst, Silvio Ofner, Beat Zehnder, René Lattmann, Kurt Hilpert, Rudolf Waditschatka, Alexander Fässler, Rolf Nussberger*†*, Christian Lehmann, Thomas Früh, Christian Leumann, Fritz Kreppelt, Kaspar Zimmermann, Thomas Oberhauser.*

Postdoctoral co-workers*: Salem Farooq* (1971 – 1973), *R. C. F. Jones* (1973 – 1974), *Koichi Hirai* (1973 – 1975), *Franz-Peter Montforts* (1976 – 1977), *Kasturi Shrinivasachar* (1976 – 1978), *Paul Naab* (1977 – 1978), *James H. Rigby* (1977 – 1978), *John Eigill Johansen* (1979 – 1980), *Günter Bartels* (1980 – 1981), *John N. Lewis* (1980 – 1981), *Anthony Davis* (1981 – 1982), *Karl Grubmayr* (1982 – 1983), *Jean C. Plaquevent* (1983 – 1984), *Sundeep Dugar* (1985 – 1986), *Wolf-Ulrich Nickel* (1985 – 1986), *Jerome F. Hayes* (1986 – 1988)

Special appreciation and acknowledgment of their exceptional role played in my laboratory over all the years are due to the two permanent members of my research group, *Jakob Schreiber* (1922 – 1992)[5]) and *Dorothee Felix*. If high experimental standards were an sustained asset of the group, it is to a large degree their merit. I also want to thank my secretary *Hermie Zass-Gächter* for her loyal and competent collaboration over so many years.

The research on the chemistry of corrins and Vitamin B_{12} in my group had been generously supported by the *Swiss National Science Foundation* and by (the former) *Ciba-Geigy AG,* Basel.

The project of finally publishing in full the author's work on the chemistry of corrins would and could not have become reality without the most generous help and sustained encouragement of *M. Volkan Kisakürek*, Editor-in Chief of *Helvetica Chimica Acta*. It is him who inspired the project in the first place, and the merit of finally accomplishing it is no less his than the author's. I want to offer *Volkan* my deepest appreciation and gratitude. *Richard J. Smith*, member of the editorial team of legendary '*Helvetica*', deserves my thanks for helping wherever he could, especially for his fine drawing of the *Figures* of Part I.

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5) *Cf.* A. Eschenmoser, '*Zum 70. Geburtstag von Dr. Jakob Schreiber*', *Chimia* **1991**, *45*, 397.