Corrin-Synthesen

Teil I

Einleitung und Übersicht

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Corrin Syntheses

Part I

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[1]) As mentioned in the *Introductory Remarks* (see preceding article), *Part I* of the series *Corrin Synthesis Parts I – VI* provides an introduction to, and an overview of, work carried out at the ETH on the synthesis of corrins in the 1960s and the first half of the 1970s. The early part of the introductory article (*Chapt. 1*, and *Sects. 1 – 4* of *Chapt. 2*) consists of the original and only slightly edited German text written by the author in the late 1970. After 2011, the manuscript was extended by adding *Sects. 2 – 7* of *Chapt. 1* and the full *Chapts. 3* and *4*; thereby, an attempt to keep the extension bilingual was given up, such that the later sections and chapters are in English only. In the *list of references* of the original German manuscript, references [1 – 42] referred exclusively to the (preliminary) publications from the ETH on the synthesis of corrins and vitamin B_{12} that had appeared in the 1960s and 1970s. This not only remains unchanged, but the list is now extended (*i.e.*, [43 – 76]) cover (in chronological order) all work accomplished at the ETH on the synthesis of corrins and vitamin B_{12}, as well as the (post-B_{12}) chemistry of corrins, corphins, and other hydroporphyrins, on chlorophylls and coenzyme F430. Finally, the list is further extended – again in chronological order – with all the Ph.D. theses [77 – 132] that were carried out in the author's laboratory in the research fields mentioned.

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1. Einleitung[1]**).** – Ab 1963 ist aus unserem Laboratorium in Form von vorläufigen Mitteilungen, Vorträgen und Essays über Untersuchungen zur Synthese von Corrinen berichtet worden. In einer Serie aufeinanderfolgender Abhandlungen sollen diese Arbeiten nunmehr abschliessend zusammengestellt und mit experimentellen Teilen vervollständigt werden. *Part I* leitet die Reihe ein und gibt einen Überblick auf den Gang der Untersuchungen und die Entfaltung des Arbeitsgebiets in den 1960er und 1970er Jahren. 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 erscheinenden Veröffentlichung sein.

1.1. *Syntheseziel Vitamin B_{12}*. Der Name Corrin[3]) steht für den Grundkörper des macrocyclischen Ligand-Systems, welches als Cobalt-Komplex im Vitamin B_{12} und in den Coenzymen B_{12} vorkommt (*Fig. 1*). Zusammen mit dem Ligand-System Porphin der Hämine, dem Chlorin der pflanzlichen Chlorophylle, dem Bakteriochlorin der Bakteriochlorophylle und dem Isobakteriochlorin des Sirohydrochlorins bildet es die Familie der bislang bekannt gewordenen porphinoiden Makrocyclen, deren natürliche Vertreter in der lebenden Natur biologisch fundamentale Funktionen erfüllen. Im Gegensatz zu den von beinahe sämtlichen Lebewesen biosynthetisierten porphyrinischen Cofaktoren werden die natürlichen Corrinoide nach heutiger Kenntnis weder von Pflanzen, noch von Tier und Mensch, sondern ausschliesslich von Mikroorganismen produziert. Umso mehr ist es bemerkenswert, von welch entscheidender Bedeutung dieser Verbindungstyp für den Menschen ist: die früher als letal geltende 'perniziöse Anämie' stellt heute eine Mangelkrankheit dar, deren Symptome durch Hydroxycobalamin in Dosen der Grössenordnung von 10^{-6} g pro Tag völlig behoben werden können.

Die Geschichte der Entdeckung des 'anti-pernious anemia factor', der Isolierung und Struktureraufklärung des Vitamins und der Coenzyme B_{12} ist ein ebenso bedeutendes wie faszinierendes Kapitel interdisziplinärer Forschung in Medizin, Biochemie, organischer Naturstoff-Chemie, chemischer Kristallographie und metallorganischer Chemie. In eigens dem Vitamin B_{12} gewidmeten Monographien ist diese

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[3]) Am 1. Europäischen Symposium über Vitamin B_{12} und Intrinsic Factor (23.–26. Mai 1956) in Hamburg von *K. Folkers* vorgeschlagen und durch Plenarabstimmung sanktioniert; vgl. [133]. Der Name impliziert die *trans*-Konfiguration des Ligand-Systems an der (*A*/*D*)-Ringverknüpfung.

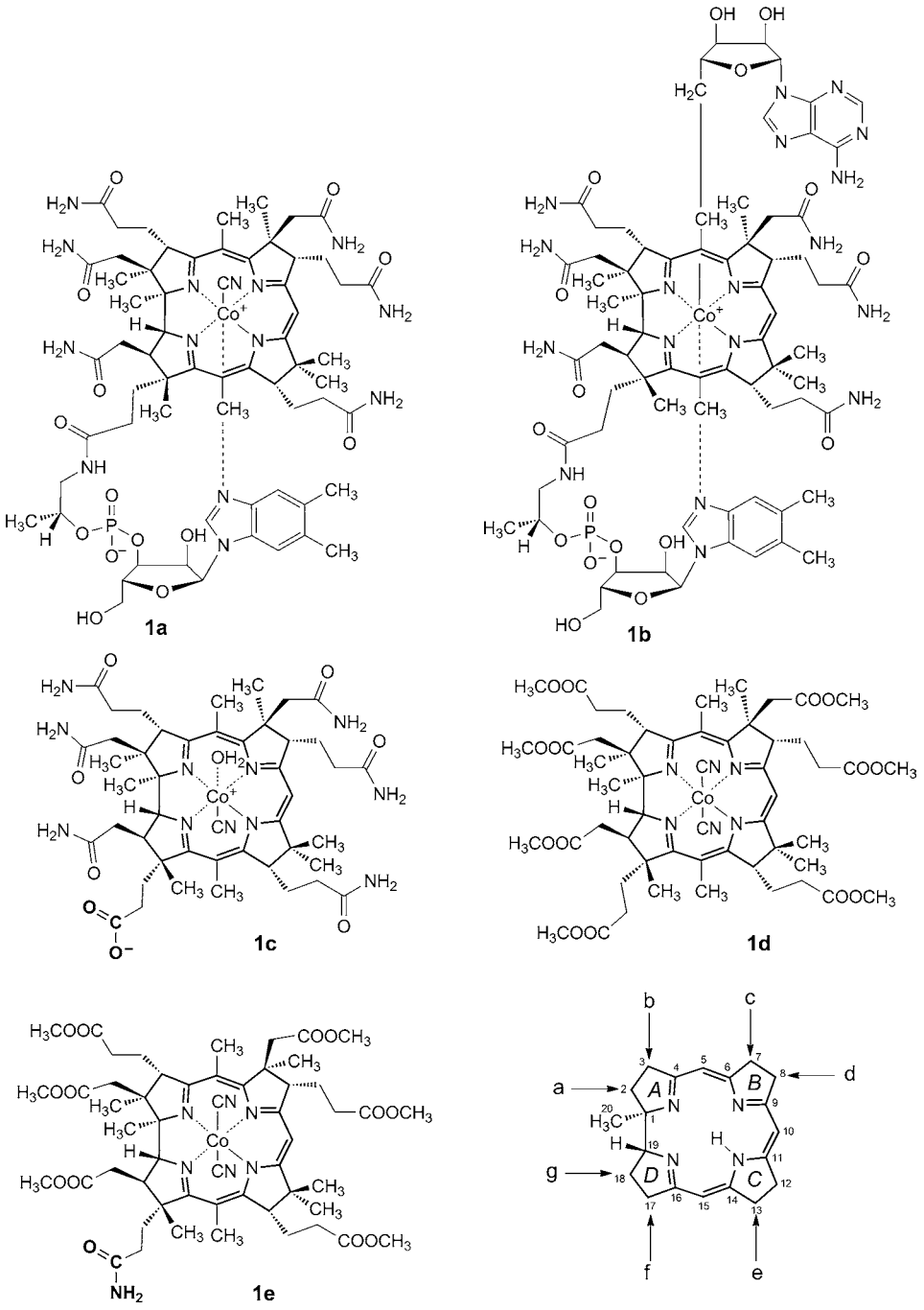

Fig. 1. *Chemical structures of vitamin B_{12}* (**1a**), *coenzyme B_{12}* (**1b**), *cobyric acid* (**1c**), *heptamethyl cobyrinate* (**1d**) ('cobester'), *and hexamethyl f-carbamidocobyrinate*

(**1e**). Compounds **1d** and **1e** are non-natural B_{12} derivatives, prepared from the vitamin in the context of the chemical synthesis of vitamin B_{12}, where they served as relay substances. The hexamethyl f-carbamidocobyrinate **1e** was the first totally synthetic intermediate to be identified with a relay compound that could be made from vitamin B_{12} and re-converted to the vitamin by partial synthesis. The formula at the lower right depicts the corrin system (including the angular Me group at C(1)) and indicates the atom numbering (1 – 20) of the ligand system, the designation of the four dihydropyrrole rings *A*, *B*, *C*, and *D*, and the positions of the acetic and propanoic acid side chains (*a* – *g*) at the B_{12}-molecule's periphery.

Table 1. *Daten zur Isolierung und Strukturaufklärung des Vitamins B_{12}*

1821	Erstmalige Beschreibung der heute als 'perniziöse Anämie' bezeichneten Krankheit beim Menschen (*Combe* [138]).
1926	Therapie der perniziösen Anämie durch Verabreichung (beträchtlicher Mengen) roher Leber (*Whipple* [139], *Minot* und *Murphy* [140].
1948	Isolierung kristallinen Vitamins B_{12} ('antipernicious anemia factor') aus Leber (*Folkers* und Mitarbeiter [51][141] sowie *Smith* und Mitarbeiter [142][5]). Entdeckung der mikrobiellen Bildung von Vitamin B_{12} (*Folkers* und Mitarbeiter [143]).
1955/56	*Röntgen*-Strukturanalyse des Vitamins B_{12} (*Hodgkin et al.* [145a – d]).
1958	Entdeckung der (Adenosyl) Coenzym-Form des Vitamins B_{12} (*Barker et al.* [146]).
1960	Isolierung der Cobyrsäure aus Faulschlamm und Partialsynthese von Vitamin B_{12} aus Cobyrsäure (*Bernhauer et al.* [147]).
1961	*Röntgen*-Strukturanalyse von Adenosyl-cobalamin (Coenzym B_{12}) (*Lenhert* und *Hodgkin* [148]).
1962	Partialsynthese von Adenosyl-cobalamin (Coenzym B_{12}) aus Vitamin B_{12} (*Johnson* und Mitarbeiter [149], *Bernhauer et al.* [150]).
1965	Isolierung metallfreier Corrinoide aus photosynthetisierenden Bakterien (*Toohey* [151]).

The milestones in the *chemical* history of vitamin B_{12} between 1948 and 1965 are the vitamin's isolation from liver in crystalline form, independently accomplished by *Folkers* [141] at *Merck* (USA) and by *L. Smith* [142] at *Glaxo* (GB), then the discovery of the microbial production of the vitamin by *Folkers* and co-workers [143], the structure determination through X-ray-analysis by *Hodgkin* in Oxford in collaboration with *White* at Princeton and *Trueblood* at UCLA [145a – d], the discovery of the (adenosyl) coenzyme form of the vitamin by *Barker et al.* [146] at Berkeley, the isolation of cobyric acid from sewage sludge and the partial synthesis of the vitamin from natural cobyric acid by *Bernhauer et al.* in Stuttgart [147], the structure determination by X-ray-analysis of coenzyme B_{12} by *Lenhert* and *Hodgkin* [148], the partial synthesis of the coenzyme from the vitamin by both *A. Johnson* and co-workers [149] and *Bernhauer et al.* [150], and finally the isolation of metal-free corrinoids from photosynthesizing bacteria by *Toohey* [151].

The highlights in *chemical synthesis* of corrins and vitamin B_{12} of the period 1960 – 1980 are compiled in *Table 2*, and the most recent accomplishments in the field (up to the year 2011) in the caption to *Fig. 2*.

Geschichte schon mehrfach umfassend dargestellt worden [133–137][4]). *Table 1* soll hier nur an die wichtigsten, und vorab aus der Sicht der organischen Naturstoff-Chemie synthetischer Richtung herausragenden Stationen erinnern[5]).

In der Entwicklung der organischen Naturstoffchemie ist der Vitamin B_{12}-Struktur eine ausserordentliche Rolle zugefallen. Bis gegen die Mitte des 20. Jahrhunderts gab es in der Naturwissenschaft nur einen einzigen Weg zur Erkennung der molekularen Struktur organischer Verbindungen: der systematische chemische Abbau und die chemische Synthese. Die Aufklärung von Naturstoff-Strukturen war für die organische Chemie ein Monopol und eine ihrer zentralen und wichtigsten Problemstellungen während *ca.* 100 Jahre. Die Etablierung der Struktur des Vitamins B_{12} auf röntgenographischem Wege durch *Dorothy Crowfoot-Hodgkin* in Oxford in Zusammenarbeit mit *John G. White* in Princeton sowie *Ken N. Trueblood* an der UCLA [145] um die Mitte der 1950er-Jahre bedeutete den endgültigen Durchbruch einer Entwicklung, die sich bereits Jahrzehnte zuvor angedeutet hatte und die schliesslich das Problemspektrum der organischen Chemie radikal veränderte: der Aufstieg der *Röntgen*-Strukturanalyse zum Status des unangefochten überlegenen Mittels der Aufklärung neuer Naturstoff-Strukturen. In der Chemie der niedermolekularen Naturstoffe trat dieser Status erstmals mit dem Vitamin B_{12} offen zu Tage, denn angesichts der Neuartigkeit und Komplexität der fast ausschliesslich[6]) röntgenographisch etablierten Struktur dieses Vitamins war den Zeitgenossen klar, dass seine Strukturaufklärung auf chemischem Wege wohl noch Jahre, wenn nicht Jahrzehnte beansprucht haben würde.

Der Szenenwechsel im Bereiche der Naturstoff-Strukturaufklärung hat naturgemäss zu Verschiebungen in Zielsetzungen auf dem Gebiete der organischen Naturstoff-Synthese geführt. Die *Woodward*'sche Synthese des Chlorophylls a [152] im Jahre 1960 erscheint heute als wohl die letzte jener grossen Naturstoff-Synthesen, welche – von ihrer Eigenbedeutung abgesehen – noch die klassische Funktion der Erbringung des abschliessenden Konstitutionsbeweises zu erfüllen hatte. Wie die 30 Jahre zuvor von *Hans Fischer* vollbrachte Totalsynthese des Hämins [153], war auch die *Woodward*'sche Chlorophyll-Synthese abschliessender Höhepunkt einer über Jahrzehnte sich erstreckenden Naturstoff-Strukturaufklärung mit chemischen Mitteln. Was

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[4]) Eine umfassende Zusammenstellung von Übersichtsartikeln, Symposium-Berichten und Monographien über Vitamin B_{12} (bis 1974) gibt *Friedrich* in [135] (S. 1); vgl. auch [133c] (S. 11 bzw. 9). Für unsere eigenen Arbeiten haben uns damals vor allem die Übersichten von *Smith* [133c] und *Bonnett* [137] wertvolle Dienste geleistet.

[5]) Über die im Jahre 1939 bereits weit fortgeschrittenen, dann aber durch den Krieg in Norwegen unterbrochenen Arbeiten von *Laland* und *Klem* zur Isolierung des 'antipernicious anemia factor', vgl. [144].

[6]) Mit chemischen Abbau-Methoden waren zwischen 1948 und 1955 von der Vitamin B_{12}-Struktur im wesentlichen die Komponenten und die Verknüpfungsart der Ribonukleotid-Kette, der periphere Teil des Ringes *C*, die peripheren Amid-Gruppen, sowie die Co-gebundene CN-Gruppe erkannt worden (vgl.[137]). Diese Ergebnisse stammten vorwiegend aus den Arbeitsgruppen von *Folkers* [154] und *Todd* [155][145b], aber auch von *Smith* [133c] und *Petrow* [156]. Ein bedeutender Beitrag der *Todd*'schen Gruppe [155b] war die Entdeckung eines erstmalig kristallisierenden Hydrolyse-Produkts von Vitamin B_{12}, der sog. 'Hexacarbonsäure' [145b]. Diese Entdeckung hatte den Durchbruch zur endgültigen röntgenstrukturanalytischen Erkennung der Vitamin B_{12}-Struktur gebracht [145].

indessen zwischen 1954 und 1956 durch die *Hodgkin*'schen *Röntgen*-Strukturanalysen fast unvermittelt zu Tage trat, war eine chemisch im wesentlichen noch unbekannte, den natürlichen Porphyrinen zwar verwandte, und doch ganz neuartige Naturstoff-Struktur mit all ihren konstitutionellen, konfigurationellen und konformationellen Einzelheiten, sozusagen eine röntgenstrukturanalytisch entdeckte, exotische Strukturinsel weitab vom Festland der bisherigen chemischen Erfahrung. Ihr Auftauchen hat die Aufgabe verdeutlicht, welche die Forschung auf dem Gebiete der Naturstoff-Synthese in der Ära der physikalischen statt chemischen Strukturaufklärungsmethoden vermehrt zu erfüllen haben wird, nämlich, über die spezifisch synthetische Zielsetzung hinaus Erfahrungsquelle der Chemie neuer Strukturtypen zu sein, Gelegenheit zu bieten, durch Begehung bisher nicht betretenen Strukturgeländes unbekannte molekulare Verhaltensweisen zu entdecken. Aus dieser Sicht stellte sich das Vitamin B_{12} Ende der Fünfzigerjahre als sozusagen obligates Zielobjekt naturstoffsynthetischer Forschung dar, als molekulare *terra incognita*, deren synthetische Erschliessung die Konfrontation mit einer Fülle neuartiger Probleme planerischer und methodischer Art mit sich bringen würde. Das Vitamin B_{12} in seiner Komplexität und Neuartigkeit stellte Gelegenheit und Herausforderung dar, die von der organischen Synthese auf dem Gebiete der niedermolekularen Naturstoffe bislang erreichten Grenzen zu überschreiten.

Schon Ende 1954, als die in Oxford unter der Leitung von *Hodgkin* und in Princeton von *White* durchgeführten röntgenographischen Untersuchungen [157] den ersten, noch unvollständigen Blick auf die Vitamin B_{12}-Struktur freigegeben hatten, trat deren Verwandtschaft mit den Porphyrinen unverkennbar zu Tage[7]); heute ist diese Verwandtschaft durch die biosynthetischen Herkunft der B_{12}-Struktur von jener des gemeinsamen biosynthetischen Vorläufer aller Porphinoide, dem *Uroporphyrinogen*, experimentell belegt[8]). Im Gegensatz zu den Porphyrinen und Chlorinen, bei deren Bildung aus Uroporphyrinogen sechs Carboxyl-Funktionen durch (zum Teil oxidative) Decarboxylierungen verloren gehen, bleiben beim Vitamin B_{12} von den insgesamt acht Carboxy-Funktionen deren sieben als Amid-Funktionen erhalten; dabei ist die Propansäure-Seitenkette am Ring *D* durch ihre amidische Verknüpfung mit der axial koordinierenden Nukleotid-Ligandkette besonders ausgezeichnet. Die Essigsäure Seitenkette am Ring *C* des Uroporphyrinogens III wird als Folge einer (redox-neutralen) Decarboxylierung zur (β-ständigen! [162]) Me-Gruppe am Ring *C*. Den klassischen Porphinoiden fremd[9]) und deshalb für die natürliche Corrin-Struktur ganz besonders charakteristisch ist der Kranz der insgesamt sieben biosynthetisch aus Adenosyl-methionin stammenden [158] zusätzlichen Me-Gruppen an der Ligand-

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[7]) Diese Verwandtschaft ist erstmals 1956 durch *Shemin* und Mitarbeiter [158] durch die klassischen biosynthetischen Einbau-Experimente von δ-Amino[1,4-$^{14}C_2$]lävulinsäure experimentell belegt worden. Über den, ab 1972 stark in Fluss geratenen Kenntnisstand zur Biosynthese von Vitamin B_{12} orientier(t)en (damals) mehrere Übersichtsartikel (vgl. insbesondere [159]).

[8]) Dass Uroporphyrinogen III der biosynthetische Vorläufer nicht nur der natürlichen Porphyrine und Chlorine, sondern auch des Vitamins B_{12} ist, war schon früh vermutet [160], doch erst 1972 [161] durch entsprechende Einbau-Versuche nachgewiesen worden.

[9]) Abgesehen vom 1973 entdeckten Sirohydrochlorin [163] und der Gruppe der sogenannten Chlorobium-Chlorophylle [164], die ebenfalls zusätzlichen Me-Gruppen an den Ringen *A* und *B*, bzw. an den Seitenketten und *meso*-Stellungen aufweisen.

Peripherie. Vier von diesen sitzen an je einem quaternär substituierten C-Atom der vier Pyrrolin bzw. Pyrrolinyliden-Ringe des Macrocyclus, wie wenn dadurch das System der Mehrfachbindungen im Molekel-Inneren eingezäunt und eine Tautomerisierung oder Dehydrierung zu pyrrolischen Ring-Strukturen verhindert werden sollte.

Von zwei *meso*-Stellungen des Corrin-Chromophors abgesehen, sitzen in der Ligand-Peripherie die Seitenketten und zusätzliche Me-Gruppen durchwegs an gesättigten C-Atomen, die – mit Ausnahme am Ring *C* – zugleich Chiralitätszentren sind. Damit ist das zentrale Ligand-System nicht wie bei den Porphyrinen flach und plansymmetrisch gebaut, sondern es weist eine räumliche Form auf, die einem von insgesamt $2^9 = 512$ [10]) formal möglichen chiralen Diastereoisomeren entspricht. Während dieser Kranz von Chiralitätszentren zwischen den Ringen *A*, *B*, *C* und *D* jeweils wie bei den Porphyrinen und Chlorinen durch eine ungesättigte C_1-Brücke unterbrochen ist, birgt der Bezirk der *A*/*D*-Verknüpfung im Corrin-Ligand eine ununterbrochene Sequenz von insgesamt sechs Chiralitätszentren an den zwei Dihydropyrrol-Ringen, die über eine (C–C)-Bindung direkt miteinander verknüpft sind. Diese Verknüpfung der Ringe *A* und *D* ist nebst dem Chromophor und den zusätzlichen Me-Gruppen das Hauptcharakteristikum des corrinischen C-Skeletts. Wegen ihrer Neuartigkeit und ihrer sowohl konstitutionellen wie auch konfigurationellen Komplexität (Ringverknüpfung durch (C–C)-Bindung zwischen tri- bzw. tetrasubstituierten stereogenen C-Atomen, sechs konsekutiv angeordnete Chiralitätszentren an nicht-annelierten, 'stereochemisch schwierigen' Fünfringen!) musste seinerzeit die Teilstruktur der (*A*/*D*)-Ringverknüpfung als eines der zentralen und wohl schwierigsten Probleme einer Vitamin B_{12}-Synthese betrachtet werden.

Den Kern der Vitamin B_{12}-Struktur bildet jedoch der mit Co komplexierte Corrin-Chromophor. Er liegt formal auf der Oxidationsstufe eines Decahydroporphyrins und ist gegenüber dem Strukturtyp des biosynthetischen Vorläufers Uroporphyrinogen um zwei Oxidationsstufen reduziert. Sein völlig auf den inneren Rand des Macrocyclus eingeschränktes Mehrfachbindung-System ist als Folge der corrintypischen Direktverknüpfung der Ringe *A* und *D* nicht cyclisch durchkonjugiert. Im weiteren Gegensatz zu den Ligand-Systemen der Porphyrine und der Chlorine weist Corrins nur eine deprotonierbare NH-Gruppe auf und nicht deren zwei.

Aus syntheseplanerischer Sicht schienen seinerzeit diese formal-strukturellen Unterschiede zu den Porphyrinen eher noch stärker ausgeprägt: ein Aufbau des Corrin-Chromophors würde unter Umständen auf überhaupt keine Vorbilder in der Porphyrinchemie zurückgreifen können; denn das Problem einer Verknüpfung von Dihydropyrrol-Ringen zu Corrinen schien jenem der Verknüpfung von Pyrrol-Ringen zu Porphinoiden zwar formal, aber keineswegs auch chemisch ähnlich zu sein. Zudem waren (*A*/*D*)-Direktverknüpfungen porphinoider Ring-Systeme damals unbekannt.

Erste Untersuchungen in Richtung auf eine synthetische Erschliessung der Verbindungsklasse der Corrine waren im Zeitraum 1955 – 1959 in Cambridge im Arbeitskreis von *A. R. Todd* [165] initiiert worden. In jenen Versuchen waren die damals noch wenig bekannten Verbindungsklassen der 1-Pyrroline (= 3,4-Dihydro-2*H*-pyrrole) und 1-Pyrrolin-*N*-oxide [166] in den Mittelpunkt eines Corrin-Synthesekon-

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[10]) Nur auf den Strukturteil des Corrin-Kerns der Vitamin B_{12}-Molekel bezogen (vgl. das Formelbild der Cobyrsäure in *Fig. 1*).

zepts gestellt worden, inspiriert nicht zuletzt durch die formal attraktive Möglichkeit, dass sich Pyrrol-Ringe mit Hilfe der Nitron-Funktion gerade auf jene zwei verschiedenen Arten verknüpfen lassen würden [167], die den beiden im Corrin-Chromophor vorkommenden Arten der Ringverknüpfung entsprechen (*Fig. 2*,*a*). Das experimentell beobachtete Verhalten der Pyrrolin-*N*-oxide erwies sich dann allerdings als zu komplex, als dass sich dieses 'Nitron-Konzept' einer Corrin-Synthese hätte verwirklichen lassen. Indessen haben diese ersten Bemühungen um eine Synthese von Corrinen zur Kenntnis der Verbindungsklasse der cyclischen Pyrrolin-oxide und Nitrone beigetragen und darüber hinaus das Problem der Entwicklung eines synthetischen Zugangs zum Strukturtyp der Corrine als besondere Herausforderung an die synthetische organische Chemie erscheinen lassen [168][11].

Das Verdienst, im Rahmen von Arbeiten zum Problem der Synthese der Corrin-Struktur ausgehend von ersten spekulativen Vorstellungen über die Biosynthese des Vitamins B_{12} (vgl. [145b]) erstmals einen Macroringschluss zwischen den Ringen *A* und *D* in Betracht gezogen zu haben, kommt *A. W. Johnson* zu. Zuvor im *Todd*'schen Arbeitskreis in Cambridge an der chemischen Bearbeitung der Vitamin B_{12}-Struktur massgeblich beteiligt, hatte Johnson nach 1955 in Nottingham mit breit angelegten synthetischen Untersuchungen auf dem Gebiete der Porphinoide und Corrinoide begonnen [170][171] und anschliessend im Laufe von zwei Jahrzehnten in konsequenter Verfolgung des Ziels der Synthese von Corrinoiden aus tetrapyrrolischen Vorläufern dem Forschungsgebiet der Corrin-Synthese entscheidende Impulse verliehen und eine Reihe grundlegender Beiträge geleistet[12]). Zu den wichtigsten gehören die Entdeckung einer ganzen Palette von oxidativen ($A \rightarrow D$)-Cyclisierungen von Tetrapyrrol-Zwischenprodukten, so die erstmals gemachte Beobachtung der Bildung eines Porphyrin-Derivats mit direkter (*A*/*D*)-Ringverknüpfung, eines sogenannten Corrols [173], sowie die Bildung von Metall-Komplexen des Strukturtyps des *trans*-Octahydro-l,19-dimethylcorrins [174] und des *Octadehydro*-l-methylcorrins [175] (*Fig. 2*,*b*, und *Table 2*). Schliesslich wurde im Zeitraum 1967 – 1971 auch das Ziel einer Synthese von Corrin-Komplexen aus Pyrrol-Vorläufern erreicht, indem es gelang, gewisse *trans*-Ni^{II}- und *trans*-Co^{III}-*octadehydro*-l,19-dimethylcorrinate katalytisch zu entsprechenden Corrin-Komplexen zu hydrieren [176][177].

Bedeutend ist auch der Beitrag, den die *Johnson*'sche Gruppe auf partialsynthetischem Gebiet erbracht hat: 1962 gelang ihr – unabhängig vom *Bernhauer*'schen Arbeitskreis [150] – die Herstellung des Coenzyms B_{12} aus dem Vitamin B_{12} [149]. Dies bedeutete die partial-synthetische Verknüpfung der einfachsten aus natürlichen Quellen erhältlichen Corrin-Verbindung, der Cobyrsäure, mit der strukturell kompliziertesten, dem Coenzym B_{12}, denn bereits zwei Jahre zuvor hatten *Bernhauer* und Mitarbeiter [147] die von ihnen aus Faulschlamm isolierte Cobyrsäure partial-synthetisch in Vitamin B_{12} überführen können (*Table 1* und *Fig. 1*). Mit diesen beiden Partialsynthesen war auch die Cobyrsäure als die primäre Zielverbindung einer totalsynthetischen Erschliessung der Naturstoff-Klasse der Corrinoide erkannt und festgelegt.

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11) Ein letzter Teil der Ergebnisse jener Untersuchungsreihe ist 1976 von *Black et al.* [169] veröffentlicht worden.

12) Für eine Übersicht über die corrinsynthetischen Arbeiten von *Johnson*, vgl. die Reihe seiner gedruckten Vorträge [171], sowie mehrere Übersichtsartikel [172].

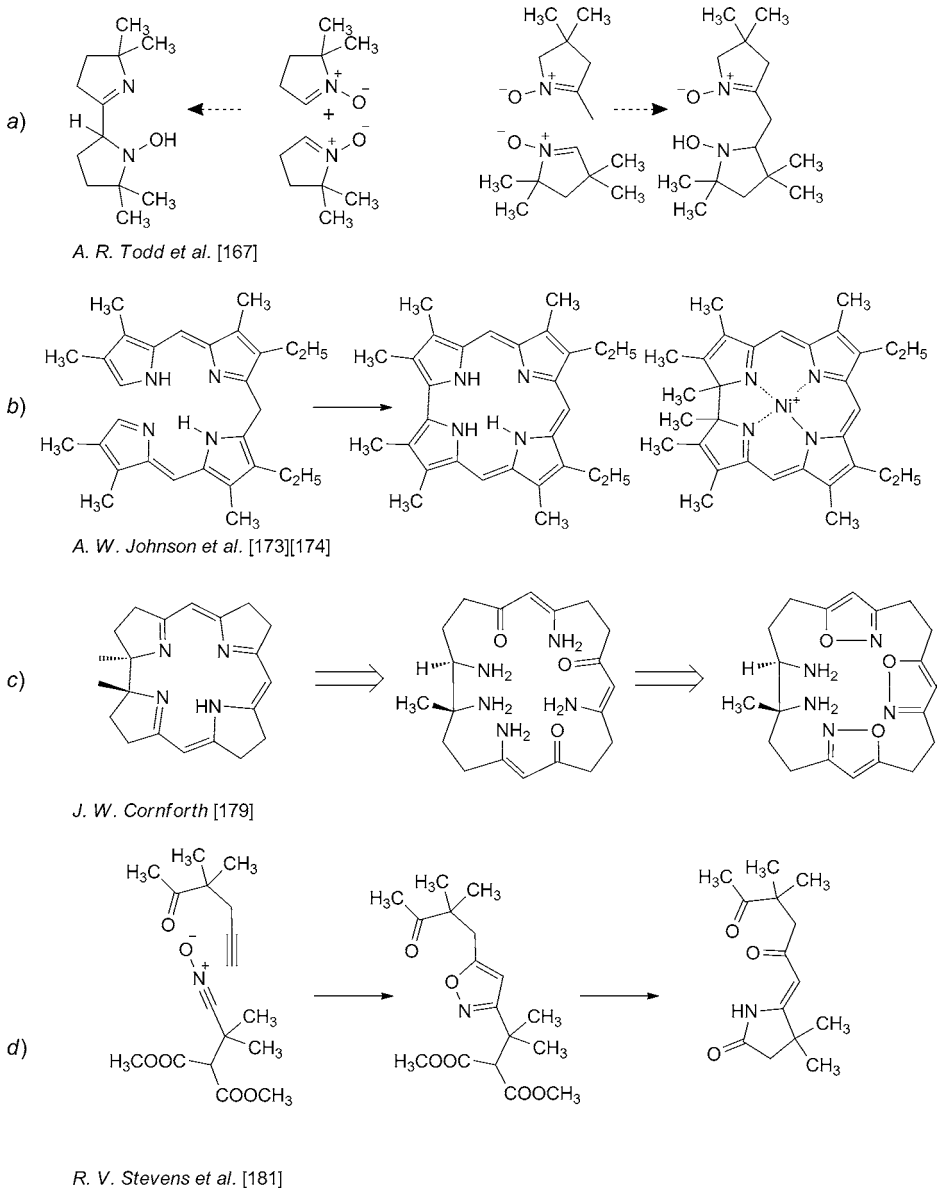

Fig. 2. *Overview of strategies for the construction of the corrin ligand system by chemical synthesis pursued from 1950s to 1970s by research groups other than those at the ETH and Harvard, work carried out by the groups of* A. R. Todd, A. W. Johnson, J. W. Cornforth, *and* R. V. Stevens. For the more recent contributions to the field of corrin and vitamin B_{12} synthesis by the research groups of *P. A. Jacobi* and *J. Mulzer* carried out in the 1990s, see below.

Once the vitamin's complete X-ray structure had become known in 1955/1956, the very first attempts toward a laboratory synthesis of the novel ligand system corrin were undertaken [167] in the laboratory of *A. R. Todd* in Cambridge, where much of the chemical groundwork towards the structure elucidation of vitamin B_{12} had been carried out in the 1950s. Even today, the strategy, on which these very first attempts were based, has to be acknowledged for its originality, 'boldness', and conceptual appeal. The plan presents itself as if the, for that time, overwhelming structural complexity and novelty of vitamin B_{12} had imposed itself upon the mind(s) of the designer(s) by calling for corresponding novelty even in a model synthesis of its structural core. At the heart of the Cambridge concept were five-membered nitrone *N*-oxides as ring building blocks, diverging in constitutional details in such a way that two different types of condensation reactions could lead to the two different kind of ring junctions that are characteristic for the corrin structure (*Fig. 2*, *a*). Retrospectively, it is not surprising that the results obtained in this experimentally difficult studies became pioneering contributions to the chemistry of cyclic nitrone *N*-oxides, rather than to corrin synthesis [168][169].

Fig. 2, *b*, shows *Alan Johnson*'s classical $A \rightarrow D$ ring closure of a 1,19-secoporphin derivative, affording a fully aromatic corrin analog, a derivative of a octadehydrocorrin ligand system called 'corrol'. This ring closure, accomplished in 1964 [173], was the first example of the formation of a direct ring junction between rings *A* and *D* within a porphinoid system, and marked the beginning of a systematic search by *Johnson*'s group for a synthesis of the corrin structure from tetrapyrrolic precursors [170][171]. This led to the synthesis of metal complexes of *octadehydro*-corrin derivatives methylated at one or both positions of the *A*/*D*-ring junction [174][175] and, in the period 1967–1971, to the synthesis of corrin complexes by catalytic hydrogenation of Ni^{II}- and Co^{III}-octadehydro1,19-dimethylcorrinates to the corresponding corrinates [176][177].

In 1962, the groups of both *Johnson* in Nottingham [149] and *Bernhauer* in Stuttgart [150] succeeded in accomplishing the chemically remarkable partial synthesis of coenzyme B_{12} from vitamin B_{12}. This synthesis connected the most complex natural corrinoid, the coenzyme, with the least complex corrinoid isolated from natural sources, cobyric acid (*Fig. 1*), since the latter had been converted to vitamin B_{12} by *Bernhauer et al.* already two years before [147] (*cf. Table 1*). These two partial syntheses defined cobyric acid as the target compound of any project that would aim at a total synthesis of vitamin B_{12}.

In contrast to the 'model-first' strategies envisaged in such projects by the groups of *Todd*, *Johnson*, and our own at the ETH, two major actors 'of the first hour' in the field – *J. W. Cornforth* since 1958 and *R. B. Woodward* since 1961 – launched their 'attacks' on B_{12} by aiming directly on the vitamin's structure without recourse to model studies by their own. Within a few years, *Cornforth* succeeded to synthesize precursors of all four rings, however, found himself running against a wall when trying to construct the direct junction of rings *A* and *D* [179]. At the bottom of his planning was the formal structural relationship indicated in *Fig. 2*, *c.* The chromophore system of the corrin core was seen as a tetraaza derivative of three macrocyclically connected β-diketone groupings, the construction of which was planned to proceed *via* correspondingly substituted isoxazole derivatives which – due

to the property of substituted isoxazoles to be convertable into vinylogous amides under reducing conditions, while being reasonably stable towards acids and bases – may serve as protected intermediates on the way to aza derivatives of these array of β-diketone functions.

It was about a decade later that the essence of this concept became the driving force of model studies that were (with reference to *Cornforth*) taken up by *Giorgio Traverso* [180] in Italy, as well as by *Robert V. Stevens* [181] at Rice University. Between 1969 and 1972, these authors demonstrated alternative pathways to one of the central intermediates of the two ETH corrin syntheses [4][14] by using the 'isoxazole route', in which the relevant isoxazole intermediates are efficiently prepared through 1,3-dipolar addition of correspondingly substituted acetylenes to nitrile *N*-oxides (*Fig. 2*, *d*). In what became an exemplary effort in synthesis, *Stevens* went on and developed the 'isoxazole route' to an efficient alternative strategy of constructing the corrin-corphin chromophore, by strategically aligning the sequence of intermediates toward a final $A \rightarrow D$ ring closure by the ETH photochemical *A*/*D*-secocorrin $\rightarrow$ corrin cycloisomerization [92]. The feasibility of this approach was demonstrated by the synthesis of Zn^{II}-1,2,2,7,7,12,12,17,17-nonamethylcorrinate [185], with its last step (the *A*/*D*-secocorrin $\rightarrow$ corrin cycloisomerization) being the same as in the ETH synthesis of the same complex (see below). Furthermore, in ingeniously conceived extensions of these model studies, *Stevens et al.* made great strides toward a corresponding alternative access to vitamin B_{12} itself [182][186]. The fact that there is no *Stevens*' vitamin B_{12} synthesis today is only due to *Bob Stevens*'s untimely death in 1984.

In the mid-1990s, two other researchers independently took up the B_{12} problem anew, both inspired by the challenge of reducing synthetic complexity through new synthetic design. They both devised alternative pathways to B_{12} ring precursors and aligned their chromophor-construction strategy again towards the final photochemical *A*/*D*-secocorrin $\rightarrow$ corrin cycloisomerization. *Peter A. Jacobi* at Wesleyan and Dartmouth, as part of his comprehensive involvement in the development of new pathways to porphinoid systems using transition metal chemistry [187], developed, in a series of models, an iterative ring coupling and formation of cyclic enamides as an efficient and general method for constructing elements of the corrin chromophore [188]. *Johann Mulzer* in Vienna, by specifically focusing on new ways to obtain ring precursors of the natural system, explored enantioselective pathways to all four rings, thereby providing a lesson of how to synthesize such building blocks of the B_{12} structure today [189].

Progress in the field of the chemical synthesis of vitamin B_{12} and/or unnatural corrins, as pursued in different laboratories, has been summarized in various review articles: first by the Russian authors *T. A. Melent'eva*, *N. D. Pekel'*, and *V. M. Berzovskii* in 1969 [190], then by *A. H. Jackson* and *K. M. Smith* in 1973 [179], in 1982 by *R. Bonnet* [191], as well as *R. V. Stevens* [192] (representative review of the Harvard/ETH work on the B_{12} synthesis), again by *Jackson* and *Smith* [193] in 1984, by *K. C. Nicolaou* and *E. Sorensen* in 1996 [194], *D. Riether* and *J. Mulzer* in 2003 [195], and *F.-P. Montforts*, *M. Osmers*, and *D. Leupold* in 2012 [196].

Im Gegensatz zu den Strategien des *Todd*'schen und *Johnson*'schen sowie des Zürcher Arbeitskreises, zielten die 1958 von *J. W. Cornforth* und die 1961 von *R. B. Woodward* begonnenen Arbeiten zur Vitamin B_{12}-Synthese vom Anfang an nicht auf vorgängige Entwicklung eines synthetischen Zugangs zum Strukturtyp des Corrin-Chromophors ab, sondern gleich auf die Bearbeitung der Synthese der B_{12}-Struktur selbst. *Cornforth*'s Ende der 1950er und anfangs der 1960er-Jahre vehement vorgenommene 'Attacke' auf die Peripherie der B_{12}-Struktur wurde in ihrer Anfangsphase mit eindrücklichen Erfolgen belohnt, gelang es doch diesem Pionier innert weniger Jahre und mit wenigen Mitarbeitern synthetische Zugänge zu potentiellen Vorläufern für sämtliche vier Ringe experimentell zu verwirklichen[13]). Eine dieser Ringvorläufer-Synthesen, jene des Ringes *C* aus (+)-Campher, wurde später von der Harvard-Gruppe übernommen und weiterentwickelt; sie sollte sich schliesslich als die Methode der Wahl für die Herstellung des Ring-*C*-Vorläufers in den Arbeiten sowohl der Harvard- als auch der ETH-Gruppe erweisen.

Im Hintergrund der *Cornforth*'schen Arbeiten zum Aufbau der Ringvorläufer hatte das in *Fig. 2*, *c*, stilisiert angedeutete 'Isoxazol-Konzept'[14]) einer Synthese des Corrin-Chromophors gestanden. In ihm kam die retrosynthetisch bedeutsame Einsicht zum Ausdruck, dass sich der Corrin-Chromophor als ein Tetraaza-Derivat dreier makrocyclisch zusammenhängender β-Diketon-Gruppierungen auffassen lässt. Unter Bezugnahme auf die Eigenschaft trisubstituierter Isoxazole, einerseits gegenüber Säuren und Basen weitgehend resistent zu sein, anderseits aber durch Reduktion leicht in β-Amino-enone überzugehen, wies das *Cornforth*'sche Synthesekonzept dem Strukturelement des Isoxazol-Ringes eine zentrale Rolle sowohl als Zwischenprodukt, wie auch Schutzfunktion zu. Experimentell angepackt worden ist dieses 'Isoxazol-Konzept' einer Corrin-Synthese rund eine Dekade später von *Traverso et al.* [180] (unter Berufung auf *Cornforth*), sowie vor allem von *Stevens et al.* [181] (*Fig. 2*, *d*). Diese Autoren haben 1969 – 1972 über die Anwendung der bekannten Isoxazol-Bildung durch 1,3-dipolare Cycloaddition von Nitril-Oxiden an Acetylene auf das Problem der Corrin-Synthese veröffentlicht und gezeigt, wie man damit zu inzwischen durch Arbeiten an der ETH bekannt gewordenen [4][14] corrinsynthetischen Zwischenprodukten gelangen kann. Seither hat *Stevens* [182] mit dieser 1,3-dipolaren Cycloaddition als Schlüsselreaktion ein leistungsfähiges Synthesekonzept für den Corrin-Chromophor entwickelt, dasselbe strategisch auf den endgültigen ($A \rightarrow D$)-Ringschluss durch photochemischen (A/D-Secocorrin $\rightarrow$ Corrin)-Cycloisomerisierung [14] (s. u.) ausgerichtet, und auf der Grundlage sorgfältig geplanter und systematisch durchgeführter Modellstudien mit breit angelegten und vielversprechenden Versuchen begonnen, eine neue Vitamin B_{12}-Synthese durch Kombination des Isoxazol-Corrin-

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13) *Cornforth* hat anfangs der 1960er-Jahre in Vorträgen über seine B_{12}-Arbeiten berichtet (vgl. [178]) und anlässlich des Symposiums 'Corrins' (Nottingham, 17.–19. Juli 1967) in einem Vortrag '*Approaches to the Synthesis of Cobalamins*' seine Arbeiten zur Synthese der Ring-Vorläufer und Ansätze zur Verknüpfung der Ringe *A* und *D* rückblickend dargestellt. Eine zusammenfassende Darstellung der *Cornforth*'schen Arbeiten zur Synthese des Vitamins B_{12} haben *Jackson* und *Smith* im Rahmen ihres Übersichtsartikels '*The Total Synthesis of Pyrrole Pigments*' [179] gegeben.

14) In *Fig. 3*, *c*, wiedergegeben gemäss Vorträgen, die von *J. W. Cornforth* am 5.2.1962 in Cambridge und am 19.7.1967 in Nottingham gehalten wurden; vgl. [179].

Synthesekonzepts mit der photochemischen (*A*/*D*-Secocorrin → Corrin)-Cycloisomerisierung zu verwirklichen[15]).

Die Barrikade, an welcher in den 1960er-Jahren die *Cornforth*'sche Attacke auf die Vitamin B_{12}-Struktur zum Stehen kam, war die (*A*/*D*)-Ringverknüpfung [179]; Versuche in mehreren Varianten, Ringvorläufer *A* und *D* konstitutions- und konfigurationsgerecht miteinander zu verknüpfen, sind damals misslungen. Demgegenüber hat die *Woodward*'sche Synthesestrategie, welche die Vitamin B_{12}-Struktur ebenfalls direkt – d. h. ohne (eigene) Modellstudien – anzielte, den Strukturbereich der Ringe *A* und *D* mit seiner *A*/*D*-Direktverknüpfung von Anfang an konsequent ins Zentrum des Syntheseentwurfs gerückt. In diesem war das konstitutionelle und stereochemische Zentralproblem der (*A*/*D*)-Verknüpfung auf raffinierteste Art integriert. Zwar stiess die experimentelle Bearbeitung der ursprünglichen Version des Synthese-Entwurfs nach drei Jahren Arbeit ebenfalls auf eine Barriere, doch hat gerade diese – gemäss *Woodward* [184] – zur Entdeckung der *Woodward–Hoffmann*-Regeln geführt. Ab 1965 sind an der Harvard die Arbeiten zur Synthese der (Harvard) *A*/*D*-Komponente auf der Grundlage einer modifizierten Planung weiter bearbeitet und mit den an der ETH ab 1960 parallel zu den Corrin-Modellstudien laufenden Arbeiten über die Synthese einer (*B*/*C*)-Komponente abgestimmt worden.

1.2. *Zur Rolle corrinsynthetischer Modellstudien im B_{12}-Synthese Projekt*. '*Das beste Modell für die Synthese eines Naturstoffs ist das Enantiomere dieses Naturstoffs*[16])' (*R. B. Woodward*). Der Verlauf der Arbeiten zur Synthese des Vitamins B_{12} bietet eine Lektion zu einer Frage, die im Bereiche der organischen Naturstoff-Synthese immer wiederkehrt: wann sind Modellversuche und Modellsynthesen notwendig und lohnend, wann sind sie entbehrlich, und wann gar irreführend? Unsere eigenen im Dezember 1959 begonnenen Arbeiten zur Synthese von Corrinen waren von der Überzeugung ausgegangen, dass die Entwicklung eines synthetischen Zugangs zum Strukturtyp des Corrin-Chromophors das primär zu lösende Problem einer Vitamin B_{12}-Synthese sei. Denn das aus synthetischer Sicht Neuartigste an der B_{12}-Struktur war das Skelett und (C=C)-Bindungssystem des Corrin-Chromophors. Unvorhergesehenes im chemischen Verhalten von Synthese-Zwischenprodukten auf dem Wege zu synthetischem Vitamin B_{12} würde sich deshalb nicht so sehr auf die Molekelperipherie, sondern vor allem auf den Chromophorbereich beziehen, und solche Verhaltensweisen würden denn auch bereits in Modellstudien zum Chromophor-Aufbau erfasst werden können. Im Laufe solcher Modellstudien würde die Frage nach der Adaptierbarkeit des Chromophor-Synthese-Konzepts auf das natürliche periphere Substitutionsmuster beurteilbar werden, ganz im Gegensatz zur Situation, wo man nach abgeschlossener Synthese peripherer Bereiche der B_{12}-Struktur vor dem Problem der erstmaligen experimentellen Realisierung eines noch arbeitshypothetischen Konzepts des Chromophor-Aufbaus stünde. In der Tat ist heute rückblickend noch immer schwerlich vorstellbar, dass ein arbeitshypothetisches Corrin-Synthese-Konzept hätte direkt mit den 'natürlichen' Ringvorläufern entwickelt, bzw. ein B_{12}-Syntheseprojekt hätte ohne corrinsynthetische Modellstudien auskommen können. Offen war im Grunde nur die Entschei-

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[15]) Über den bis März 1979 erreichten Stand dieses Syntheseprojekts, vgl. [183].

[16]) Zutreffend bei Verwendung achiraler bzw. racemischer (oder dann *entsprechend enantiomerer*) Reagentien, Katalysatoren und Lösungsmittel, *etc.*

dung darüber, ob Modellstudien zu Beginn oder in einer späteren Phase eines solchen Projekts durchzuführen seien.

Es ist dies der Zusammenhang, in welchem die 1965 erfolgte Vereinbarung über die Zusammenarbeit der B_{12}-Forschungsgruppen an der Harvard und der ETH zu sehen ist. Die bis dahin in den beiden Laboratorien durchgeführten Arbeiten hatten sich sowohl in ihrer unmittelbaren Zielrichtung, als auch in ihren Ergebnissen als perfekt komplementär erwiesen: die Harvard-Gruppe hatte bereits wichtige Erfahrungen auf dem Wege zu einer die Ringe *A* und *D* enthaltenden (*A*/*D*-Dilactam)-Komponente gemacht, und die ETH-Gruppe hatte nebst einer Synthese des Ring-*B*-Vorläufers die Erfahrung über einen in Modellstudien entwickelten Corrin-Synthesetyp vorzuweisen, der klar auf eine Synthese der Cobyrsäure nach dem Konzept der Vereinigung zweier bicyclischer Teilstücke (*A*/*D*- und *B*/*C*-Komponenten) übertragbar erschien. Die Zusammenarbeit sah vor, dass die Harvard-Gruppe sich auf die Herstellung der *A*/*D*-Komponente konzentrieren, die ETH-Gruppe die *B*/*C*-Komponente bereitstellen, und hierauf beide Forschungsgruppen unter gegenseitigem Austausch der beiden Komponenten sich gemeinsam mit dem Problem von deren Vereinigung nach dem Vorbild der Corrin-Modellsynthese aus dem Jahre 1964 befassen würden. Das gesteckte Ziel wurde dann 1972 auch tatsächlich erreicht, wobei nun aber die zahlreichen unvorgesehenen Entwicklungen, die sich auf dem Wege zu diesem Ziel einstellten, im Jahre 1968 zur Realisierung einer alternativen Corrin-Modellsynthese, und damit zum Vorbild einer entsprechend alternativen, ebenfalls 1972 vollendeten Variante der (damals noch formalen) Vitamin B_{12}-Synthese führten. Die beiden Varianten unterschieden sich in der Strategie des Aufbaus der zentralen Corrin-Struktur und vor allem in der Chemie der finalen Ringschlussreaktion: diese erfolgte zwischen den Ringen *A* und *B* in der Variante, welche der ursprünglichen Planung entsprach ('*A*/*B*-Variante'), und zwischen den Ringen *A* und *D* in der Variante, deren Strategie sich erst im Laufe der Arbeit am B_{12}-Synthesprojekt ergab ('*A*/*D*-Variante', vgl. *Kap. 3* unten)). *Fig. 3* illustriert die beiden Corrin-Ringschluss-Varianten der Vitamin B_{12}-Synthese und ihre entsprechenden Vorbilder, die beiden alternativen Modell-Corrin-Synthesen.

Lohnend, wie die corrin-synthetischen Modellversuche für das Projekt der Vitamin B_{12}-Synthese auch gewesen sein mögen, weist die Geschichte dieses Syntheseprojekts doch auch mindestens ein eindrückliches Beispiel dafür auf, wie die strukturelle Vereinfachung eines Syntheseziels durch Übergang von der komplexen Zielstruktur auf ein Modell in gewissen Fällen eine chemisch entscheidende Verarmung der Synthese-Problematik in sich schliessen kann. So ist jene Kondensationsmethode, die abschliessend sämtliche Ringverknüpfungsprobleme des Chromophor-Aufbaus beider B_{12}-Synthesen gelöst hat ('Sulfid-Kontraktion *via* oxidative und alkylative Kupplung' [17]), nicht im Zuge der corrin-synthetischen Modellstudien entwickelt worden; sie war vielmehr die Folge einer 'heuristischen Zwangslage', in die man erst bei der Bearbeitung der eigentlichen Naturstoff-Struktur geraten war. Das diesem Kapitel vorangestellte Zitat über Modellversuche besteht letztlich zurecht, auch wenn es Scherz und Wirklichkeit zu vermischen scheint.

Synthesestudien an peripher vereinfachten Corrin-Strukturen mögen zwar in den Anfängen der synthetischen Corrin-Chemie hauptsächlich die unmittelbare Funktion naturstoffsynthetischer Modellversuche erfüllt haben, ihre Ziele und Folgen gingen

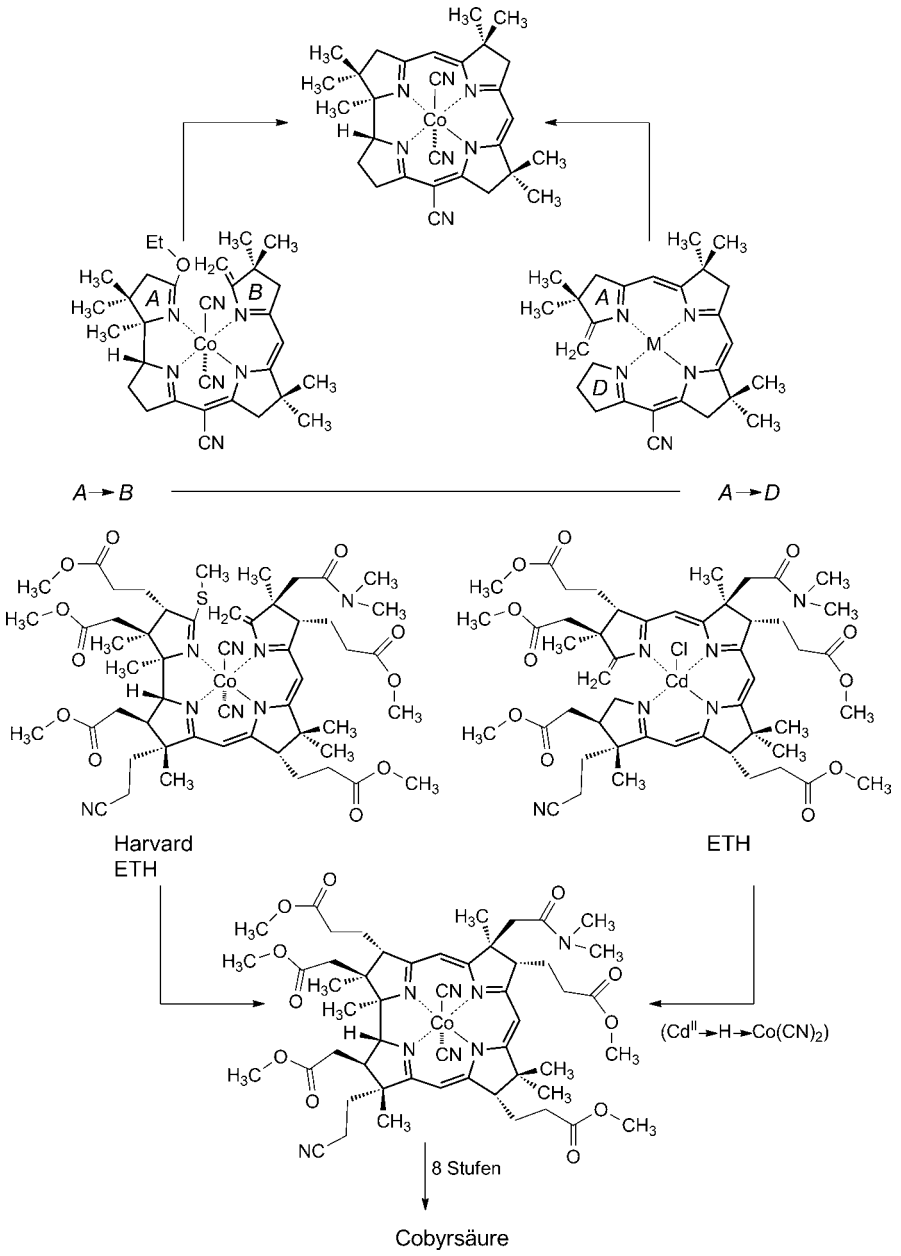

Fig. 3. *Fig. 3* juxtaposes the final steps of two ETH model corrin syntheses with the ring-closure steps of the two variants of the Harvard/ETH synthesis of vitamin B_{12}.The two strategies define synthetic paths towards secocorrin intermediates as substrates for a final secocorrin → corrin ring closure between either the rings *A* and *B* and, alternatively, between the rings *A* and *D*, by two chemically vastly different

ring-closure reactions. The two strategies of corrin-chromophore construction in the two variants of the vitamin B_{12} synthesis reflect the two approaches for corrin synthesis developed in the model studies. Half a century ago, the structural complexity and novelty of vitamin B_{12}'s corrin ligand rendered model studies of chromophore construction indispensible for any project that was aiming at a total synthesis of the vitamin. None of the two B_{12} syntheses eventually realized could have been accomplished – at least within the time they actually required – without the comprehensive information the model studies made available to the ETH and, therefore, also to the Harvard group. This is especially true of the photochemical variant of the vitamin B_{12} synthesis.

The corrin model studies influenced and assisted the planning and execution of the two B_{12} syntheses in a multitude of ways. The assistence consisted in information on preparative procedures and the scope of the C,C-coupling by imido ester/enamine and thioimido ester/enamine condensations, spectroscopic and chemical properties of hemicorrinoids, *A*/*B*- and *A*/*D*-secocorrinoids, as well as corrinoid chromophore systems in their neutral, protonated, and metal-coordinated forms, information on the properties of highly labile hemicorrinoid and *A*/*B*-secocorrinoid imido esters and thioimido esters, complexation and decomplexation procedures involving metal ions, and secocorrinoid and corrinoid ligand systems, the relative susceptibility of the corrin ring's three *meso*-positions to electrophilic substitutions, procedures for the introduction of Me groups in these positions and, finally, the 'targeted discovery' of the photochemical *A*/*D*-secocorrin → corrin cycloisomerization in a model series without which there would be no photochemical variant of the B_{12} synthesis.

Essential for the B_{12} project as these model studies may have been, the actual work on the synthesis also provided instructive examples of how a model study in natural-product synthesis can oversimplify the synthetic challenge posed by the natural target structure and become misleading, examples that lend support to a legendary *Woodwardian* statement: '*The best model for the synthesis of a natural product structure is its enantiomer*'[16]). The perhaps most important case is the construction of the hemicorrinoid *B*/*C* component, a central intermediate in the construction of the corrin ligand in both model corrin syntheses, as well as in both variants of the B_{12} synthesis. The final method for the construction of the vinylogous amidine system, the basic structural element of the corrin chromophor, had not been born in a model synthesis, but rather in the natural series in an effort to overcome the *failure* of joining the ring *B* precursor with the precursor of ring *C* by the method of imino ester (or thioimido ester)/enamine condensation. The solution of the central problem of coupling a thiolactam with an enamide to form a vinylogous amidine system was found in the method of C,C coupling *via* 'sulfide contraction'. It was eventually this methodology by which, in both variants of the B_{12} synthesis, all three hemicorrinoid ring junctions between rings *A*, *B*, *C*, and *D* were constructed.

Another instructive case of failure in attempting to apply a methodology developed in the model synthesis was the complexation of free corrin ligands with Co^{II} perchlorate in an inert solvent (to be followed by treatment with cyanide and finally by $Co^{II} \rightarrow Co^{III}$ oxidation with air): perfectly working in the model series, but in the natural series producing complex mixtures containing oxidatively damaged ligands. The main reason for this discrepancy had to be the CN group at C(15) of the

chromophor in the model corrin; there, it may protect the corrin chromophor against oxidation by virtue of its pronounced electrophilicity, while the chromophor of the natural series is devoid of such protection. As the Harvard group discovered, replacing the Co^{II} perchlorate by Co^{II} chloride and using a hydroxylic solvent was the solution of this important problem.

Numerous problems that arose in the B_{12} project as the consequence of the specific *nature* of the peripheral substituents at the natural corrin chromophor could clearly not be dealt with in the model studies. The most prominent of these problems was the necessity of keeping the carboxy function in position f at ring *D* differentiated from the beginning to the very end of the synthesis in order to be eventually able to arrive at the structure of cobyric acid (however, see the amendment to this statement in captions to *Table 2* and *Fig. 26*).

In the 1970s and 1980s, work on the so-called 'post-B_{12}' problems on corrinoids at the ETH was mainly driven by the question of what kind of chemistry might be available to *Nature* for creating the notorious *A*/*D* junction in the biosynthesis of vitamin B_{12}. From there, the research gradually shifted to questions referring to the etiology of the corrinoid type of biomolecular structure. The observations made in these post-B_{12} studies are not a minor part of the full harvest of insights gained from the comprehensive research project that originally had started as a model study for the chemical synthesis of vitamin B_{12} [70][76].

aber – wie man zum Teil erst heute zu erkennen vermag – weit darüber hinaus. Mit zur Zielsetzung dieser Arbeiten gehörte ursprünglich auch die Herstellung vereinfachter corrinoider Ligand-Systeme zum Zwecke systematischer Untersuchungen über die Chemie der Corrine im Hinblick auf die ursprünglich so rätselhafte Chemie der biologischen B_{12}-Funktionen. Diese Zielsetzung ist in der Folge dann allerdings in den Hintergrund getreten, und zwar vor allem aus zwei Gründen: Zum einen hat bereits im Jahre 1964 *G. Schrauzer* [197] die wichtige Beobachtung gemacht, dass selbst strukturell sehr einfache Co-Komplexe wie jene des Dimethylglyoxims[17]) die besondere metallorganische Chemie der Corrinoide überraschend weitgehend zu simulieren vermögen. Die seither in zahlreichen Laboratorien im Hinblick auf den Mechanismus B_{12}-katalysierter Enzym-Reaktionen durchgeführten Untersuchungen mit solchen und anderen 'B_{12}-Modellen' hat wertvolles Wissen über potentiell B_{12}-relevante Co-Komplex-Chemie erbracht [198]. Zum anderen ist im Laufe der Zeit das mikrobiologisch produzierte Vitamin B_{12} derart leicht zugänglich geworden, dass bald einmal der Verwendung des Naturstoffs als Ausgangsmaterial corrin-chemischer Untersuchungen kaum mehr etwas im Wege stand[18]). Kürzlich ist gar eine Arbeitsrichtung entstanden, in der Vitamin B_{12} als Katalysator präparativ-chemischer Umsetzungen vorgeschlagen und verwendet wird [201][202].

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17) In Anlehnung an Cobalamin 'Cobaloxime' genannt [197].

18) Ein wichtiges, aus Vitamin B_{12} durch säurekatalysierte Methanolyse zugängliches, kristallisierendes Cobalamin-Derivat ist der erstmals in unserem Laboratorium von *Reinhart Keese* [199] hergestellte Cobyrinsäure-heptamethyl-ester ('Cobester') Vgl. *Fig. 1*. Über die reduktive Umwandlung von dessen Carbonsäure-ester-Gruppen in Me-Gruppen vgl. [200].

Der vielleicht wichtigste und über die Rolle naturstoffsynthetischer Modellstudien hinausgehende Beitrag corrinsynthetischer Forschung bezieht sich auf die biologisch-chemische Fragestellung nach dem Ursprung der Corrin-Struktur. Vorab ist damit die Rolle gemeint, welche die Corrin-Synthetik im Zusammenhang mit der Aufklärung der mikrobiellen Biosynthese der natürlichen Corrinoide erfüllen kann. Der bisherige Verlauf der um 1972 mit neuem Impuls einsetzenden und vor allem in den Laboratorien von *A. R. Battersby* [159a][203], *A. I. Scott* [159b][204], *V. I. Bykhovsky* [205a], *D. Arigoni* [205b] sowie von *G. Müller* [205c] vorangetriebenen Bearbeitung dieses komplexen Problems bietet das Bild eines Reigens bedeutender Ergebnisse, Entdeckungen, dramatischer Überraschungen wie auch interpretatorischer Irrtümer. Insofern eine möglichst weitgehende, chemische Vorkenntnis der Bildungsmöglichkeiten einer Naturstoff-Struktur eine wichtige Voraussetzung für die Planung gezielter Experimente in der Erforschung von deren Biosynthese darstellt, und sich offenbar auch bei der Erforschung der Biosynthese des Vitamins B_{12} die *A*/*D*-Verknüpfung als ein Kernproblem herausstellt, waren von einer systematischen corrinsynthetischen Aufdeckung des Spektrums potentiell biomimetischer Reaktionswege zur corrinischen *A*/*D*-Verknüpfung Einsichten und Impulse für die biosynthetische Corrin-Forschung zu erwarten. Das Ineinandergreifen von Synthese- und Biosynthese-Problematik in der Naturstoff-Chemie tritt hier im Falle der corrinoiden Naturstoffe besonders offen zutage.

Von vielleicht noch weitgehenderer Auswirkung als solch chemische Impulse zur Aufklärung der B_{12}-Biosynthese könnten Einsichten sein, die sich aus den Ergebnissen gezielter Corrin-Synthetik im Hinblick auf die Frage [28][32] nach dem eigentlichen Ursprung der Corrin-Struktur, d.h. dem *Ursprung der Biosynthese* dieses Strukturtyps ergeben könnten. Probleme des chemischen Ursprungs und der Evolution biosynthetischer Reaktionswege sind innerhalb der Chemie der Naturstoffe naturgemäss bislang kaum berührt worden; aus solchen Fragestellungen dürfte aber in absehbarer Zukunft der organischen Naturstoff-Synthetik eine naturwissenschaftlich relevante Funktion erwachsen. Es sind nicht zuletzt die Ergebnisse der Corrin-Synthetik, die auf diese Aufgabe der organischen Naturstoff-Chemie mit Nachdruck hinweisen.

Die wichtigsten Stationen, welche die synthetischen Corrin- und B_{12}-Arbeiten in den Laboratorien von *Johnson*, *Woodward*, *Stevens* und an der ETH Zürich in den 1960er und 1970er Jahren durchlaufen haben, sind in *Tab. 2* chronologisch zusammengestellt. In den nachfolgenden Kapiteln wird eine im Wesentlichen ebenfalls chronologisch geordnete Übersicht über die aus dem ETH-Laboratorium stammenden Beiträge gegeben, soweit sie Modell-Corrine betreffen. Bezüglich der Arbeiten der in *Tab. 2* aufgeführten Forscher sei auf deren eigene, zusammenfassenden Darstellungen in der Literatur [171][182][208] hingewiesen.

2. Die Zürcher Corrin-Synthesen (1960 – 1970). – 2.1. *Corrin-Synthese* via *(*A → B*)-Ringschluss: Die ursprüngliche (*A/D + B/C → *ADCB)-Strategie des Chromophor-Aufbaus nach dem Verfahren der Imidoester–Enamin-Kondensation*.

Am Ausgangspunkt der Zürcher Arbeiten über die Synthese von Corrinen (Dezember 1959) hatten die in *Fig. 4* skizzierten Überlegungen gestanden, welche man heutzutage als (partielle) retrosynthetische Analyse der Corrin-Synthese apos-

Table 2. *Übersicht auf die im Zeitraum 1960–1980 auf dem Gebiete der chemischen Synthese von corrinoiden Verbindungen und von Vitamin B_{12} erzielte Ergebnisse* (über Ergebnisse, die Partialsynthesen von B_{12}-Derivaten betreffen, vgl. *Table 1*)

1964	Synthese von Ni^{II}- und Dicyano-Co^{III}-Komplexen des *rac*-15-Cyano-7,7,12,12,19-pentamethylcorrins[19]) *via* (*A* → *B*)-Cyclisierung durch Imidoester–Enamin-Kondensation [3–6][77–79] [83] Synthese von 8,12-Diethyl-2,3,7,13,17,18-hexamethylcorrol und Ni^{II}-8,12-Diethyl-2,3,7,8,12,13,17,18-*octadehydro*-l,2,3,7,13,17,18,19-octamethyl-corrinat[20]) durch oxidative (*A* → *D*)-Cyclisierungen von Biladien (ac)-Vorläufern (*Johnson et al.* [173][174]).
1967	Synthese des *rac*-Dicyano-Co^{III}-1,2,2,7,7,12,12-heptamethylcorrinats *via* (*A* → *B*)-Cyclisierung durch Imidoester–Enamin-Kondensation [8][85][88][90] Synthese eines metallfreien Corrins (15-Cyano-1,2,2,7,7,12,12-heptamethylcorrinium-Kation) *via* (*A* → *B*)-Cyclisierung durch Sulfid-Kontraktion [9][88][95]. Katalytische Hydrierung von Ni^{II}-8,12-diethyl-2,3,7,8,12,13,17,l8-octadehydro-1,3,7,13,17,19-hexamethylcorrinat (19) zu einem Gemisch diastereoisomerer Ni^{II}-corrinate (*Johnson et al.* [176]).
1968	Synthese eines *Corphin*-Komplexes (Pd^{II}-complex of 2,2,7,7,12,12,17,17-octamethylcorphin) [12][86][100].
1969	Synthese des Ligand-Systems des *rac*-2,2,7,7,12,12-Hexamethyl-1-methyliden-1,19-secocorrins mittels der 'Sulfid-Kontraktions Methode' und anschliessender (*A* → *D*)-Ringschluss durch die photochemische (*A*/*D*-Secocorrin → Corrin)-Cycloisomerisierung [14][15][17][98][99][101] [113].
1971	Synthese von Ni^{II}- und Dicyano-Co^{III}-Komplexen des 1,19-Dimethylcorrins durch katalytische Hydrierung der entsprechenden Octadehydrocorrin Komplexe (*Johnson et al.* [177])
1972	Im Februar 1972 komplementär vollendete (formale) Synthesen der Cobyrsäure (und implizite Vitamin B_{12}) auf zwei verschiedenen Wegen: (*A*/*D* + *B*/*C*)-Variante *via* (*A* → *B*)-Cyclisierung (' Harvard/ETH Variante') [13][17][87][92][97][208] und (*B*/*C* + *A* + *D*)-Variante *via* photochemische (*A*/*D*-Secocorrin → Corrin)-Cycloisomerisierung ('ETH-Variante') [17][19] [20][24][29][91][97][102][103][107] (vgl. *Kap. 3*, unten).
1975	Synthese von Ni^{II}-1,2,2,7,7,12,12,17,17-nonamethylcorrinat-perchlorat *via* reduktiv-elektrochemische (*A* → *D*)-Cyclisierung des entsprechenden 18,19-Didehydro-l-methyliden-l,19-secocorrinats [26][28][114].
1976	Vitamin B_{12} aus total synthetischer Cobyrsäure (*Woodward* [209][21])). Aufbau des Chromophor-Systems von 2,2,7,7,12,12,17,17-Octamethyl-l-methyliden-1,19-secocorrin nach dem Isoxazol-Konzept (*Stevens et al.* [181][182]). Bildung des Ni^{II}-15-Cyano-1,2,2,7,7,12,12-heptamethylcorrinats durch elektrochemische oxido-reduktive (*A* → *D*)-Cycloisomerisierung des entsprechenden 17,18-Dehydro-1-methyliden-1,19-secocorrinats [27][28][110].
1977	(Säure/Base)-induzierte (*A* → *D*)-Cyclisierung des 19-Carboxy- sowie 19-Formyl-Derivats von Ni^{II}-5-Cyano-l,2,2,7,7,12,12-hexamethyl-l-methyliden-l,19-secocorrinat-perchlorats [28][31][114].
1980	Synthese von Ni^{II} und Dicyano-Co^{III}-Komplexen des 19-Acetyl-1,2,2,7,7,12,12,17,17-octamethyl-corrins *via* '(Dihydrocorphinol → Corrin)-Umlagerung' [38][39][114].

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[19]) Der Corrin-Ligand von **7d** ist hier (im Verstoss gegen Nomenklaturregeln [207]) als 15-Cyano-7,7,12,12,*19-methyl*corrinat benannt um dessen enger struktureller Zusammenhang mit der Konstitution sämtlicher später synthetisierter Corrin-Derivate graphisch zu wahren.

[20]) In der hier gemäss [207] verwendeten Porphyrin- und Corrin-Nomenklatur sind die von *Johnson* als '*Tetra*dehydro'-corrine bezeichneten synthetischen Verbindungen Derivate des 2,3,7,8,12,13,17,18-*Octa*dehydro-corrins.

[21]) Im Jahre 1976 vollendet, jedoch erst drei Jahre später veröffentlicht [209].

Table 2. *Achievements in Chemical Synthesis of Corrins and of Vitamin B_{12} in the Laboratories of* A. W. Johnson, R. B. Woodward, R. V. Stevens, *and the Author between 1960 and 1980* (for partial syntheses within the natural B_{12} family, see *Table 1*).

1964	Synthesis of the Ni^{II}- and Co^{III}-complex of *rac*-15-cyano-7,7,12,12,19-pentamethyl*corrin*[19]) *via* (*A* → *B*)-ring closure by imido-ester/enamine condensation [3–6][77–79][83] Synthesis of 8,12-diethyl-2,3,7,13,17,18-hexamethylcorrol und Ni^{II}-8,12-diethyl-1,2,3,7,13,17,18,19-octamethyl-2,3,7,8,12,13,17,18-octadehydro-corrinate[19]) (*A. W. Johnson et al.* [173][174]).
1967	Synthesis of *rac*-dicyano-Co^{III}-1,2,2,7,7,12,12,-heptamethylcorrinate *via* *A* → *B* ring closure by imido-ester–enamine condensation [8][85][88][90] Synthesis of the metal free *rac*-15-cyano-1,2,2,7,7,12,12-heptamethylcorrinium cation [9][88][95]. Formation of (mixtures of) diastereoisomeric Ni^{II}-corrin complexes by hydrogenation of corresponding Ni^{II}-octadehydrocorrinates (*Johnson* and co-workers [175][176]).
1968	Synthesis of a *corphin* complex (Pd^{II}-2,2,7,7,12,12,17,17-octamethylcorphinate) [12][86][100].
1969	Synthesis of the ligand system of *rac*-2,2,7,7,12,12-hexamethyl-1-methylidene-1,19-secocorrin by the method of '*sulfide contraction*' and final *A* → *D* ring closure by the photochemical *A/D-secocorrin* → *corrin cyclosisomerization* [14][15][17][98][99][101][[113].
1971	Synthesis of the Ni^{II}-and Co^{III}-complexes of 1,19-dimethyl-*corrin* by catalytic hydrogenation of the corresponding octadehydro complexes (*A. W. Johnson* [177]).
1972	Two (formal) total syntheses of vitamin B_{12} *via* two concurrently finished variants: one *via* joining an *A*/*D* with a *B*/*C* component, followed by closing the corrin ring between rings *A* and *B* (the variant accomplished at Harvard [208a–c][13][17][87][92][97]), and the other by joining rings *A* and *D* with the (same) *B*/*C* component, followed by closing the corrin ring between rings *A* and *D* by the photochemical *A*/*D*-secocorrin → corrin cycloisomerization (variant accomplished at the ETH) [17][19][20][24][29][91][97][102][103][107] (*cf. Chapt. 3* below).
1975	Synthesis of Ni^{II}-1,2,2,7,7,12,12,17,17-nonamethylcorrinate perchlorate *via* electrochemically reductive *A* → *D* cyclization of the corresponding 18,19-didehydro-1-methylidene-1,19-secocorrinate [26][28][114].
1976	Conversion of totally synthetic cobyric acid into totally synthetic vitamin B_{12} (*Woodward* and *Wuonola* [209][20])). Construction of the chromphor system of 2,2,7,7,12,12,17,17-octamethyl-1-methylidene-1,19-secocorrin) by the isoxazol route (*Stevens et al.* [181][182]). Formation of Ni^{II}-15-cyano-1,2,2,7,7,12,12-heptamethylcorrinate *via* electrochemical oxido-reductive *A* → *D* cycloisomerization of the corresponding 17,18-dehydro-1-methylidene-1,19-secocorrinate [27][28][110].
1977	Corrin synthesis by acid/base-catalyzed *A* → *D* cycloisomerization of 19-carboxy-1-methylidene and 19-formyl-1-methylidene-*A*/*D*-secocorrin complexes [28][31][114].
1980	Formation of 19-acetyl-Ni^{II}- and Co^{III}-*corrin* complexes *via* a biomimetic 'dihydrocorphinol → 19-acetylcorrin rearrangement' [38][39][114].
1981 (1988)	The reaction of heptakis(*cyanomethyl*)cobyrinate with the free nucleotide chain of B_{12}'s nucleotide loop leads to the attachment of the nucleotide chain to the f-propanoic acid side chain with high regioselectivity, affording – after ammonolysis – vitamin B_{12} [70][131][210]

The reference in *Table 2* to *Robert V. Stevens*' achievement of the year 1976 (the synthesis of 2,2,7,7,12,12,17,17-Octamethyl-1-methylidene-1,19-secocorrin *via* the isoxazole approach [181][182][185]) has to be complemented by referring to *Stevens*' conversion of the Zn^{II} complex of this nonamethyl-*A*/*D*-secocorrin to the Zn^{II} complex of the corresponding nonamethylcorrin by the photochemical *A*/*D*-secocorrin → corrin cycloisomerization [186]. To the best of the author's knowledge, this is the only case where the photochemical *A* → *D* ring closure was performed outside ETH.

trophieren würde. Jene Überlegungen fussten in der Einsicht, dass ein Corrin-Chromophor-System **4a** bzw. **4b** auf dem gleichen Oxidationsniveau liegt wie ein Struktur-Ensemble des Typs des Dilactams **4f** und des Succinimids, d.h., dass letztere als Produkte einer formalen Hydrolyse von **4b** *via* **4c**, **4d** und **4e** betrachtet werden können[22]). Das Problem eines synthetischen Aufbaus des Corrin-Chromophors liess sich demzufolge als das Problem einer Umkehr dieser stufenweisen Formal-Hydrolyse auffassen, d.h. als Problem C,C-verknüpfender Kondensationen zwischen Imid- bzw. Lactam-(C=O)-Gruppen und geeignet aktivierten, d.h. enolischen oder enamischen C-Zentren. Die hierzu als Hilfselemente vorgesehenen Carbonsäureester-Gruppen hätten dabei – nebst ihrer Aktivierungsfunktion bei Synthesebeginn – die Aufgabe zu erfüllen, in Zwischenprodukten des Typs **4c** und **4e** die Lage der enaminischen Doppelbindungen zu fixieren, wobei sie nach vollendetem Corrin-Chromophor-Aufbau durch Hydrolyse und (protonkatalysierte) Decarboxylierung wieder leicht entfernbar sein würden.

Die in *Fig. 4* skizzierte retrosynthetische Formalhydrolyse des Corrin-Chromophors macht in ihrer Zergliederung des makrocyclischen C-Skeletts automatisch halt vor der Direktverknüpfung der Ringe *A* und *D*. Hierin liegt der Ursprung der am Ausgangspunkt unserer Corrin-Arbeiten gestandenen Strategie, wonach ein die Ringe *A* und *D* umfassendes Dilactam-Derivat **4f** dem Ensemble der Ausgangs- bzw. Zwischenprodukte einer Corrin-Synthese anzugehören habe: zwar werde das Primärproblem corrinsynthetischer Modellstudien die Entwicklung einer Chromophoraufbau-Methodik sein, wichtiges Problem einer Cobyrsäure- bzw. Vitamin B_{12} -Synthese werde jedoch der Aufbau der zugehörigen *A*/*D*-Komponente mit all ihren stereochemischen Implikationen darstellen.

Von wesentlicher Bedeutung in der in *Fig. 4* skizzierten Syntheseplanung war die sorgfältige Wahl der Konstitution des Syntheseziels. Das unsubstituierte Corrin-System **4a** würde von vornherein nicht in Frage kommen, denn aus der Chemie des Vitamins B_{12} war bereits damals bekannt, dass die natürlichen Corrinoide in basischem Medium im Ring *B* leicht oxidiert werden. Entsprechende Vorgänge in peripher durch geminale Alkyl-Substituenten nicht blockierte Corrinen würden zu vermutlich irreversibler Bildung pyrrolischer Teilstrukturen im Bereich der Ringe *B* und *C* führen, und solche zusätzliche Komplikationen würden sehr wohl den Versuch eines Aufbaus des Corrin-Chromophors aus sozusagen 'unfairen' Gründen zu Fall bringen können.

Als erstes Syntheseziel wurde deshalb das *Pentamethyl*-corrin **4g** ausgewählt; in ihm sind C(7) und C(12) in den Ringen *B* und *C* durch geminale Me-Gruppen gegenüber oxidativer Pyrrolisierung geschützt, und an C(1) sitzt – wie im Vitamin B_{12} – eine anguläre Me-Gruppe. Die geminal substituierten Positionen und die anguläre Me-Gruppe liegen asymmetrisch, analog wie in den natürlichen Corrinoiden; diese Asymmetrie würde zwar für die Entwicklung von Methoden des Chromophor-Aufbaus möglicherweise eine Erschwernis bedeuten, anderseits aber auch regioselektive Kondensationsreaktionen an den beiden Lactam-Funktionen in Dilactamen des Typs

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[22]) Das Konzept der formal-hydrolytischen Strukturzerlegung zwecks Planung eines Synthesewegs (in heutiger Sprache: *retrosynthetische* Analyse) ist 1917 von *R. Robinson* in seiner Tropon-Synthese verwendet worden; vgl. hierzu [28].

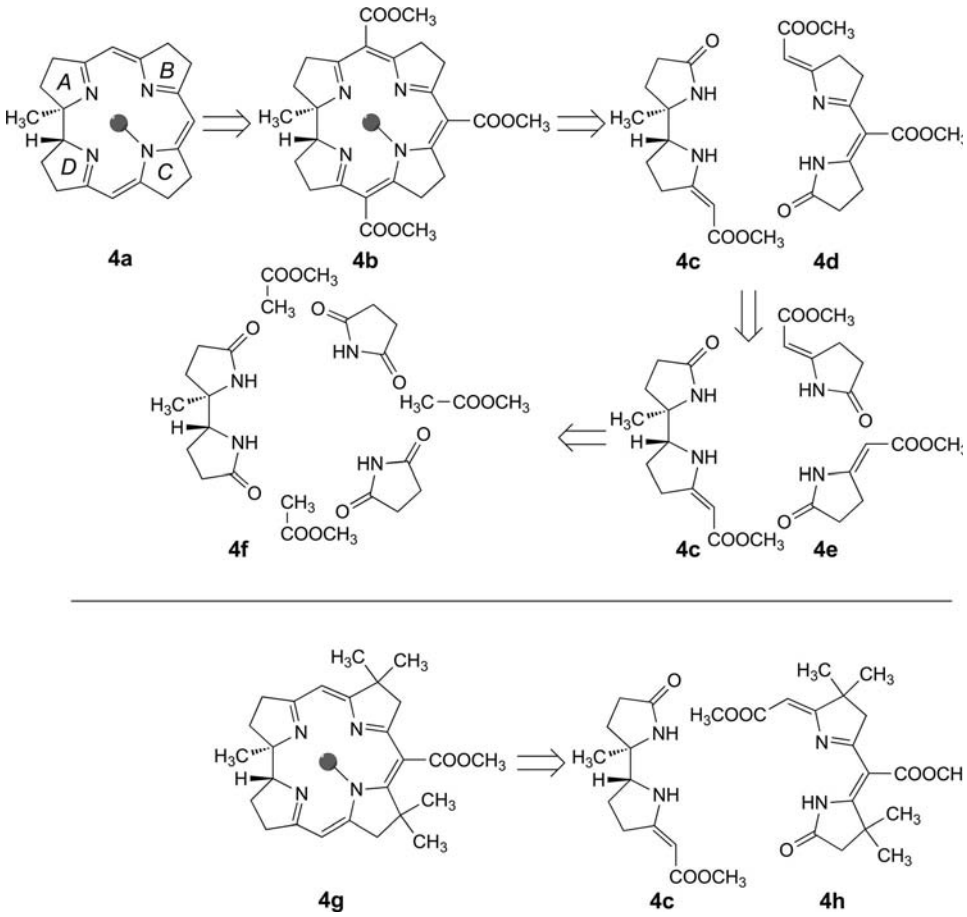

Fig. 4. Our original ideas about how to approach the synthesis of a corrin (today one would refer to 'retrosynthetic analysis of the corrin structure') were based on a concept that, probably for the first time, was applied by *Robert Robinson* as early as 1917 in his classical work on the synthesis of tropinone [211]: a target structure is dissected by steps that correspond to a 'formal hydrolysis' into intermediates or starting materials, and the synthesis of the target structure will consist in the chemical reversal of these hydrolytic steps. For an adoption of this concept to a synthesis of the corrin structure, it was important to first extend the latter (*i.e.*, **4a**) into its equivalent **4b** which then by two 'hydrolytic dissections' would become equivalent to the ensemble **4c** + **4d**, and by further such steps *via* the ensemble **4c** + **4e** + **4e** equivalent to the ensemble composed of the dilactam **4f**, two succinimide and three methyl acetate molecules, all involved ensembles remaining on the oxidation level of the corrin structure **4b**. The dissection of the target structure by formal hydrolyses encompasses the entire corrin chromophore, but does not include the dilactam structure **4f** that contains the direct junction between rings *A* and *D*. It was, therefore,

clear from the beginning that the task of synthesizing a corrin structure should be divided into three separate problems: first, synthesis of an *A*/*D* component in its dilactam form, second, preparation of a hemicorrinoid *B*/*C* component of type **4d**, and third, joining the latter to an *A*/*D* component modified into a structure of type **4c**. To serve as a model of the natural system, the dilactam form of the *A*/*D* component should be the *trans*-isomer and be asymmetrized through an angular Me group at one of the ring junctions, such that reactions at one of the lactam C=O groups (as one leading to **4c**) could be achieved under regiocontrol. Furthermore, rings *B* and *C* should contain quaternary centers in positions that are quaternary in the natural system. This would also preclude the intrinsic danger that rings *B* and *C* of a peripherally unsubstituted corrin system would become dehydrogenated to pyrrolic structural elements under the influence of air in basic medium. Such reasoning led us to structure **4g** as the first choice of a model target, the juxtaposition of the bicyclic components **4h** and **4d** in the *Figure* pointing to how the two components will be joined.

A major advantage of the plan was seen in the general stability to be expected for intermediates that contain lactam groups and are conjugatively stabilized enamines. What furthermore could be expected was a high propensity of such intermediates to crystallize. The task of connecting the pieces by a process that would correspond to a 'reversal of hydrolysis' would require a transient activation of the lactam C=O groups. The general concept envisaged to achieve such activation is outlined in *Fig. 5*.

4f ermöglichen. Die Formelbilder **4h** und **4d** stehen für die Endstufen in der ursprünglichen Version der experimentell anzugehenden Synthesestrategie.

Das zentrale Element der Gesamtstrategie liegt darin, dass die vorgesehenen Zwischenprodukt-Typen entlang des Chromophor-Aufbaus durchwegs den Strukturtypen sekundärer Amide und Imide, bzw. deren vinylogen Analoga, angehören, d.h. Stoffklassen , die bekanntlich stabile, meist leicht zu isolierende, da im allgemeinen gut kristallisierende, Verbindungen darstellen. Bei Syntheseprojekten in bislang unbegangenem Strukturgeländen kann solche Zwischenprodukt-Stabilität für den Erfolg des Unternehmens entscheidend sein, indem sie immer wieder strukturelle Standortsbestimmungen entlang des Syntheseweges ermöglicht. Rückblickend, insbesondere wenn man z.B. an das 'Nitron-Konzept' eines Corrin-Aufbaus denkt (vgl. *Fig. 3*, *a*), hat dieser Aspekt zweifellos auf dem Weg zum ersten synthetischen Corrin eine nicht zu unterschätzende Rolle gespielt.

Das Konzept einer Corrin-Synthese *via* stabile Zwischenprodukte verlangte notwendigerweise die Aktivierung der elektrophilen Reaktivität der reaktionsträgen Amid- bzw. Imid-(C=O)-Gruppen im Hinblick auf C,C-verknüpfende Kondensationen mit nucleophilen C-Zentren. In der *Fig. 5* ist das generelle Aktivierungs- und Kondensationskonzept illustriert, welches zum Rückgrat der ursprünglichen Corrin-Synthese-Planung in unserem Laboratorium wurde. Sein Kern ist der Aufbau des Vinamidin-Chromophors[23]), des charakteristischen Strukturelements des Corrin-Chromophors, durch den Reaktionstyp der Imidoester–Enamin-Kondensation.

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[23]) 'Vinamidin' = 1,5-Diazapentadien, Strukturelement der vinylogisierten Amidin-Gruppe, vgl. [212].

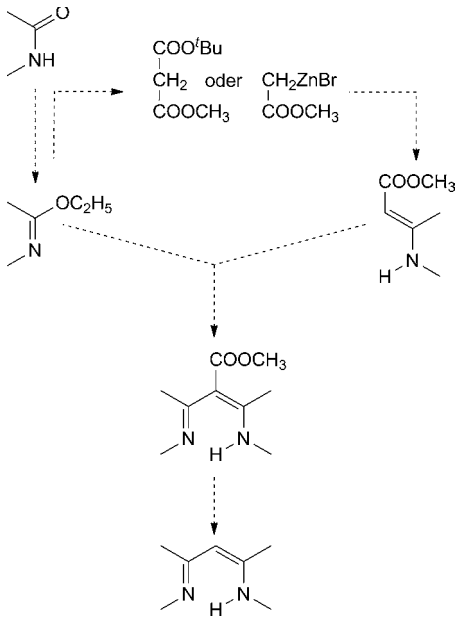

Fig. 5. *General concept for synthesizing a vinylogous amidine system* (a 'vinamidine' [212]), *the threefold repeating structural element of the corrin chromophor: activation of a lactam* (or imide) *C=O group by* O-*alkylation, condensation of the resulting imido ester with* tert-*butyl methyl malonate* (to be followed by selective mono-decarboxylation), *or with methyl bromoacetate under the conditions of a* Reformatzki *reaction.* Imido-ester/enamine condensation of the resulting enamino ester with its imido-ester precursor is assumed to afford a vinylogous amidine, with the COO group in its *meso*-position being expected to be removable by acid-catalyzed decarboxylation.

Since the classical work of *Pinner* [213] on the chemistry of imido esters ('imino ethers') and their preparation from corresponding nitriles, it has been known that this class of compounds displays a high electrophilic reactivity at the imido-ester C-atom, especially under acid catalysis. Furthermore, it had long been known that Ag salts of imides, as well as amides, in reacting with alkyl halides can become alkylated preferably at the O-atom (and not at the N-atom) to form the corresponding imido esters [214]. However, as we demonstrated in our work, *Hans Meerwein*'s triethyloxonium tetrafluoroborate ('*Meerwein* salt') [215], a reagent that had been discovered in 1937 [215a], but whose applicability in organic synthesis seemed – apart from a few exceptions [216] [217] – still unrecognized in the early 1960s, proved to be the by far most reliable reagent for converting amide and lactam groups into corresponding imido-ester groups [4].

Zu den Quellen dieses Aufbaukonzepts gehörten einerseits die auf *Pinner*'s [213] klassische Untersuchungen zurückgehende Kenntnis der im Vergleich zu Amid-(C=O)-Gruppen stark erhöhten nucleophilen Reaktivität von Imidoester-Gruppen, und

anderseits die schon seit langem für Einzelfälle dokumentierte Eigenschaft der Ag-Salze von Imiden und Amiden, durch Alkyl-halogenide vorwiegend am O-Atom alkyliert zu werden [214]. Im Laufe unserer Arbeit hat sich dann aber herausgestellt, dass die bereits 1937/39 von *Meerwein et al.* [215] beschriebene, um 1960 jedoch in der präparativen Chemie noch kaum beachtete Methode der *O*-Alkylierung von Amid- und Lactam-Gruppen für das Gelingen dieses Imidoester-Konzepts eines Corrin-Chromophor-Aufbaus entscheidend war, und dass diese Reaktion eine zuverlässig in hohen Ausbeuten und unter mildesten Bedingungen verlaufende Methode der (Lactam → Imidoester)-Umwandlung darstellt. Zwar war die im Vergleich zu einer entsprechenden Amid-(C=O)-Gruppe höhere Reaktivität einer Alkoxy-carbimido-Gruppe gegenüber Nukleophilen bereits seit den *Pinner*'schen Arbeiten [213] bekannt, doch war diese Eigenschaft nur in vereinzelten Fällen als Neubildung einer C,C-Bindung beobachtet worden [216][217][24]). In Naturstoff-Synthesen wurde dieser Reaktionstyp bisher nicht eingesetzt.

Am Anfang unserer experimentellen Arbeiten über die Synthese eines Corrins stand eine umfassende Vorstudie über die Herstellung und die Eigenschaften von Imidoester-Derivaten des α,α-Dimethylsuccinimids, Succinimids, Pyrrolidin-2-ons und entsprechenden vinylogisierten Ester- oder Nitril-Derivaten (*Fig. 6*). Hieraus resultierte die entscheidende Erfahrung, dass zwar Imidoester-Derivate des Typs **6a** oder **6c** (cyclische *N*-Acyl-imidoester- und vinylogisierte Derivate) C,C-Kondensationen als *Knoevenagel*- oder *Reformatzky*-Reaktionen zu entsprechenden vinylogisierten Ester-Derivaten des Typs **6b** oder **6d** eingehen, nicht aber – wie dies die Syntheseplanung von *Fig. 4* (**4e** + **4e** → **4d**) verlangt hätte – mit Folgeprodukten solcher Aufbaureaktionen, d.h. mit entsprechenden C^{β}-(Methoxycarbonyl)-enamid Derivaten **6b** und **6d**. Da kaum zu bezweifeln war, dass die Ursache u. a. auf die Minderung der Nukleophilie des Enamin-C-Zentrums den beiden endständigen Acyl-Substituenten in den 'Enaminen' **6b** und **6d** zurückzuführen ist, war der einfachste nächste Planungsschritt die Entfernung der MeOCO-Gruppe z.B. aus der zentralen Kondensationskomponente **6b**, eine Modifikation die – im Gegensatz zu einer Entfernung der *N*-Acyl-Gruppe – mit der generellen Syntheseplanung immer noch vereinbar sein würde. Experimentell zeigte sich aber, dass auch das modifizierte Methyliden-lactam **6e** weder als solches, noch in seiner NH-deprotonierten Form eine C,C-Kondensation mit dem Imidoester **6g** oder mit *N*-Acyl-imidoestern eingeht. Die Katalyse solcher Kondensationen durch Säure war infolge der unter solchen Bedingungen sehr leicht erfolgenden Dimerisierung von **6e** (s.u.) nicht gangbar.

Obwohl auch das Methyliden-lactam **6e** die Erwartungen nicht erfüllte, erkannte man immerhin das Potential dieser Verbindung für den Aufbau einer entsprechend modifizierten Version **6f** der ursprünglich geplanten bicyclischen *B*/*C*-Komponente **4d.** So gering und nicht unbedingt zwingend der erfolgte Planungsschritt **6b** zu **6e** auch war, hatte er doch für unsere Arbeit entscheidende Folgen: Die beiden enamidischen Verbindungen **6e** und **6f** wurden zu den zentralen Ausgangs- und Zwischenprodukten sämtlicher Arbeiten unserer Forschungsgruppe über die Synthese von Modell-

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[24]) Es waren dies die Arbeit von *Petersen und Tietze* aus dem Jahr 1959 [216a] und jene von *Plieninger et al.* von 1962 [216b]. Unseres Wissens hatte erstmals *S. Petersen* cyclische Imidoester für C,C-Kondensationen (mit enolisierbaren Carbonyl-Verbindungen) eingesetzt (Vortragsreferat aus dem Jahre 1952 [217]).

Corrinen und Corphinen (vgl. unten, sowie *Teile II*, *IV*, *V* und *VI* dieser Reihe). Die in der ursprünglichen Planung erhobene Forderung nach einer (dort durch Konjugation mit MeOCO-Gruppen garantierten) Fixierung der Enamin-(C=O)-Bindung in exocyclischer Lage war in den beiden Methyliden-lactamen **6e** und **6f** durch die Stellung der geminalen Me-Gruppen gewährleistet.

Hier ist einzuschieben, dass das auch nach der Realisierung der ersten Corrin-Synthese (s. u.) noch weiter verfolgte Ziel der Herstellung einer *B*/*C*-Komponente durch Imidoester–Enamin-Kondensation durch die im unteren Teil der *Fig. 6* dargestellte Synthese von **6k** *via* die Reaktionssequenz **6e** → **6g** → **6h** → **6i** und **6i** + **6a** → **6k** schliesslich doch noch erreicht wurde[25]). Abgesehen davon, dass dieser Zugang zu einer *B*/*C*-Komponente sich als durch Nebenreaktionen präparativ eingeengt erwies (vgl. Fig. 24 im *Teil II* dieser Reihe), kam er ohnehin zu spät, um noch in einer Corrin-Synthese Anwendung zu finden.

Sowohl im obigen, als auch im nachfolgenden Zusammenhang war schliesslich die Beobachtung wichtig, dass C^{β}-Cyano-enamine – wie z. B. das aus **6e** (oder auch Pyrrolidin-2-on) *via* Kondensation mit 2-Cyanoesssigsäure-*tert*-butyl-ester und nachträglicher Hydrolyse und Decarboxylierung zugängliche β-Amino-nitril **6i** (welches als Ketimin Tautomer stabiler ist) – C,C-Kondensationen des Typs **6i** + **6a** → **6k** mit *N*-Acyl-Imidoestern eingehen, dies im wichtigen Unterschied zu entsprechenden *N*-Acyl-β-enamino-ester-Derivaten. In solchen Kondensationen sind die Nitrile generell reaktiver als die entsprechenden Methylester. Die Präsenz einer CN-Gruppe an C(15) aller unserer synthetischen Modell-Corrinen ist denn auch auf diese Tatsache zurückzuführen.

Aus all diesen Gegensätzen und Überlappungen zwischen retrosynthetischer Analyse und experimentellen Beobachtungen ergab sich schliesslich der in *Fig. 7* wiedergegebene Syntheseplan. Darin weist die *A*/*D*-Komponente **7a** nicht – wie ursprünglich vorgesehen – eine anguläre Me-Gruppe am Ring *A* auf, sondern eine solche in *isomerer* Lage am Ring *D*. Grund hierfür war die auf dem Wege zur *A*/*D*-Komponente gemachte Erfahrung, dass eine solche Komponente mit der Me-Gruppe am Ring *D* sich als deutlich leichter herstellbar erwies; auf die Chemie der Corrin-Synthese-Endstufen würde ein solcher Unterschied in der Lage der Me-Gruppe keinen Einfluss haben. *Für die Endstufen* **7a** + **7b** → **7c** → **7d** *war zu erwarten*, *dass die konjugierte Imidoester-Gruppe im Ring* C *der* B/C-*Komponente* **7b** *eine eindeutig höhere elektrophile Reaktionsbereitschaft aufweist als die isolierte Imidoester-Gruppe im Ring* A *der* A/D-*Komponente* **7a**, *und deshalb unter den Reaktionsbedingungen einer intermolekularen Imidoester-Kondensation die* A/D-*Komponente selektiv mit der Imidoester-Gruppierung der* B/C-*Komponente* **7b**, *und nicht mit der eigenen Imidoester-Gruppe kondensieren wird.* Da das Produkt **7c** einer solchen Vereinigung von *A*/*D*- und *B*/*C*-Komponente zwischen den Ringen *C* und *D* ein vermutlich wenig stabiles tetracyclisches Ligand-System sein dürfte, sollte dieses durch Komplexierung mit einem geeigneten Übergangsmetall-Ion abgefangen, und der abschliessende intramolekularen Corrin-Ringschluss zwischen den Ringen *A* und *B* in einem

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[25]) Diese von *Werner Häusermann* [84] in der ersten Hälfte des Jahres 1965 erzielten Ergebnisse sind seinerzeit nicht publiziert worden, sie werden jedoch im *Teil II* dieser Reihe im Detail beschrieben.

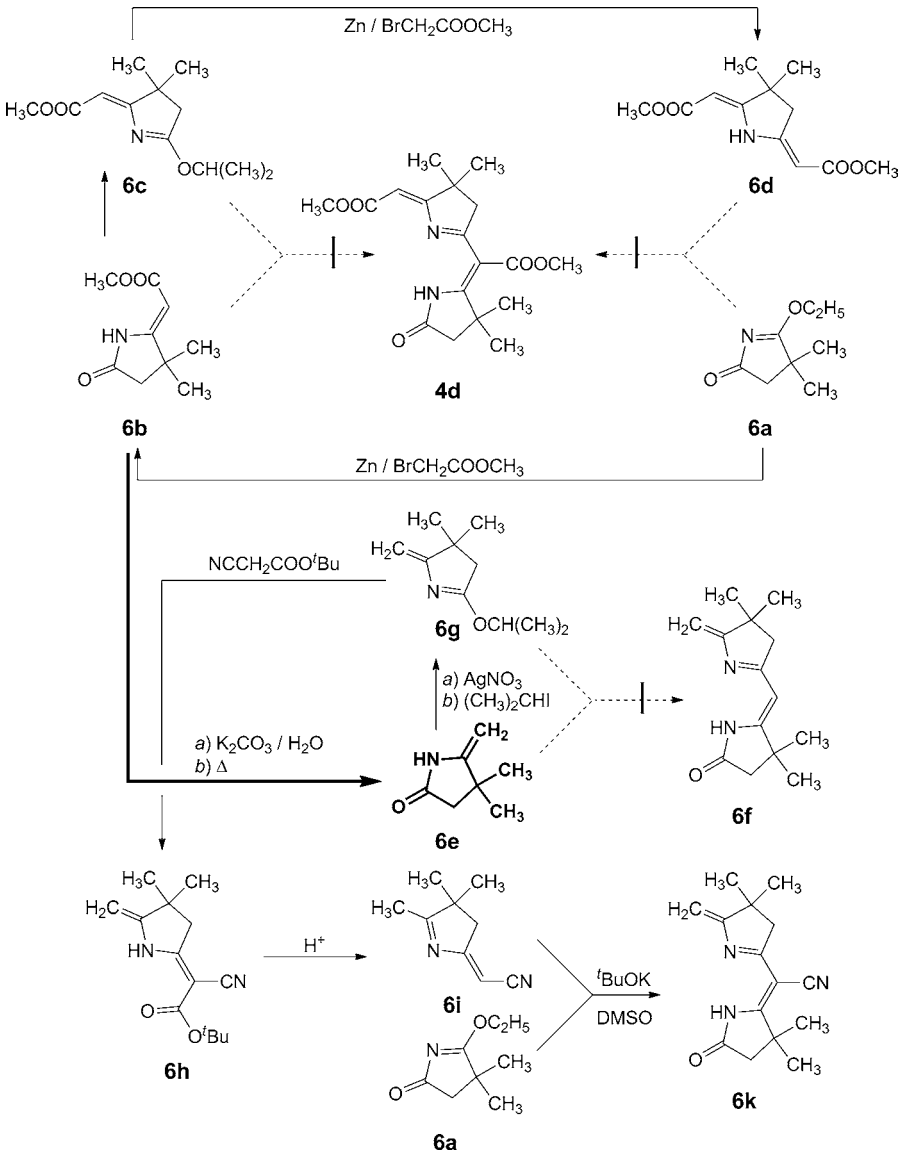

Fig. 6. The planning for the first corrin synthesis as discussed in the context of *Figs. 4* and *5* had not been a quick shot, but rather the result of an extended analysis of the problem which took its time. In December 1959, this analysis had matured to the extent that *Rolf Scheffold* [77], soon afterwards joined by *Ehrhard Bertele* [78], both Ph.D. students, could start first exploratory experiments of a systematic study on the scope of C,C-bond formation by imido-ester/enamine C,C-condensations, involving starting materials such as succinimide, α,α-dimethylsuccinimide, pyrrolidin-2-one, and imido esters derived from their Ag salts (see *Part II* of this series). *Fig. 6*

illustrates the earliest promising results (compounds such **6a**, **6b**, **6c**, and **6d**), as well as the first and most important failure, namely, the failure to produce **4d** by the two imido-ester condensations indicated. What is also shown – by a bold arrow – is the conclusion drawn from those failures, namely, to drop the COO function of amino-ene ester **6b** to give the enamide **6e**, hoping that, by the removal of the electrophilic MeOCO substituent, the nucleophilicity of the enamide C-atom would be increased, such that imido-ester/*enamide* condensations with imido esters **6c**, or with *N*-acylimido esters of type **6a**, might succeed. This proved *not* to be the case under either basic or acidic conditions, the latter having been found to be inapplicable because of the propensity of **6e** to dimerize under acidic conditions with great ease. The new disappointment notwithstanding, the monocyclic enamide **6e** happened to become the central monocyclic building block of all our work on model corrins, one that conceptually, as well as experimentally, paved the way to its hemicorrinoid analog **6f**, the compound that was to serve as (the lactam form of) the *B*/*C* component in all our model corrin syntheses. The path by which **6f** was first prepared (see *Fig. 8*) was rather tedious and less than satisfactory, yet made the corrin synthesis of 1964 possible. Three years later, **6f** could be synthesized from two molecules of **6e** by a highly efficient method (*cf. Fig. 18*).

After 1964, exploratory work on imido-ester/enamine condensations continued [84]. It finally led to the reaction sequence **6e** → **6g** → **6h** → **6i** and **6i** + **6a** → **6k** (bottom of *Fig. 6*), involving a variation of the original plan for the synthesis of a *B*/*C* component. The difference consisted in using **6i** as condensation partner instead of **6d**, with **6i** containing a CN substituent instead of a MeOCO group in the enamine system and a methylidene group instead of a (methoxycarbonyl)methylidene grouping at ring *B* (enamine **6i** was found to be more stable as ketimine tautomer). However, **6k** never found practical use as a *B*/*C* component of a corrin synthesis, since its preparation could not compete with the (later variant) of the synthesis of **6f**. Throughout the exploratory work, C^{β}-cyano enamines were found to be much more reactive in imido ester/enamine condensations than corresponding C^{β}-methoxycarbonyl enamines; this – by the way – is the reason why all our model corrin syntheses contain a CN substituent in the *meso*-positions between rings *C* and *D* (*cf. Fig. 3*).

Reaction conditions [78][84]: **6a** [78] → **6b**: $BrCH_2COOCH_3$/Zn, $HgCl_2$, N_2, benzene/Et_2O, reflux; 50%; **6b** → **6c**: a) $AgNO_3$, EtOH, NH_3 → silver salt; 85%; b) MeCHI, $CHCl_3$, r.t./in the dark; 50%; **6c** → **6d**: $BrCH_2COOCH_3$/Zn, $HgCl_2$, N_2, benzene/Et_2O, reflux; 43%; **6b** → **6e**: a) K_2CO_3, MeOH/H_2O, 45° → carboxylic acid; 79%; b) 140°; 93%; **6e** → **6g**: a) MeCN, $AgNO_3$, $EtN(^iPr)_2$ → Ag salt; 89%; b) Me_2CHI, r.t./in the dark; 83%; **6g** → **6h**: a) *tert*-butyl 2-cyanoacetate, Et_3N, N_2, 75° → bis-adduct; 60%; b) 170°/0.01 Torr; 88%; **6h** → **6i**: CF_3COOH, 60°; 70%; **6i** + **6a** → **6k**: ^{t}BuOK, DMSO, 55°; 34%. For an alternative synthesis of ene-lactam **6e**, see *Fig. 10*.

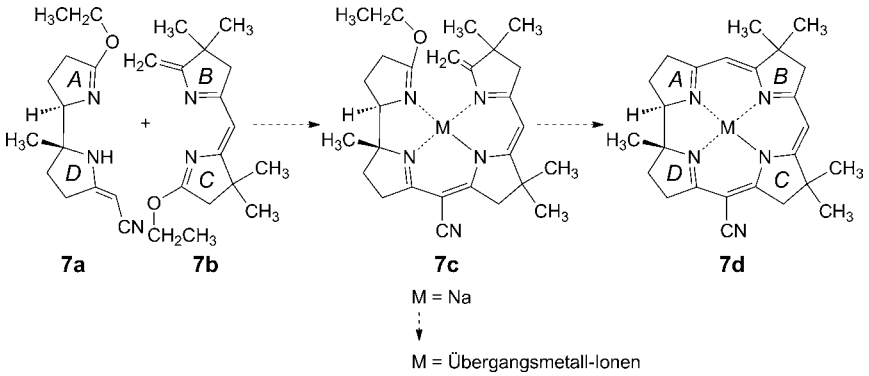

Fig. 7. Out of the extensive interplay between retrosynthetic reasoning and observations made in exploratory experiments emerged the final version of the *A*/*D* + *B*/*C* strategy for the first corrin synthesis: the *A*/*D* component **7a** is to be condensed with the *B*/*C* component **7b** by an intermolecular imido-ester/enamine condensation between rings *D* and *C*, to be followed by a complexation of the (presumably) labile *A*/*B*-secocorrinoid condensation product **7c** with a transition-metal ion, and finally forming the macrocyclic ring by linking rings *A* and *B* within a robust transition metal *A*/*B*-secocorrin complex to give a corrin complex **7d** by an intramolecular imido ester/enamine condensation. The ring closure would be be assisted by the template effect of the coordinating metal ion that would posit the involved reaction centers in close proximity. Importantly, *the imido-ester group in ring* C *of the* B/C *component as part of a conjugated electrophilic* π*-system is expected to be more reactive than the isolated imido-ester group of the* A/D *component; therefore, conditions of an imido-ester/enamine condensation should lead to a coupling of the two components between rings* C *and* D*, and not to a reaction of the* A/D *component with itself.*

The *A*/*D* component **7a** bears its angular Me group at ring *D* and not at ring *A*, as it had been envisaged in the original plan (*cf. Fig. 4*). This change in target structure was decided as a consequence of an observation made while experimentally exploring the path toward an *A*/*D* component: *A*/*D* component **7a** can be constructed much more efficiently than the isomer with the angular Me group at ring *A*. This change was not expected to have any influence on the final two condensations steps.

According to the nomenclature rules for corrins [207] (*Fig. 1*), the ligand system of **7d** would have to be named 5-cyano-1,8,8,13,13-pentamethylcorrin, and not 15-cyano-7,7,12,12,19-pentamethylcorrin. The inofficial numbering reflects itself in the 'wrong' formula presentation **7d** and is chosen here for the sake of presenting and discussing the corrin formulae of the tetra-, penta-, and heptamethyl series (*cf. Fig. 8*) uniformly from the same perspective.

The first synthesis of a corrin complex, that of the Ni^{II}-15-cyano-7,7,12,12,19-pentamethylcorrinate perchlorate **8zn** (= **7d**; for the nomenclature, see above), was achieved in February 1964 [4]. The main actors were *Rolf Scheffold* [77], *Erhard Bertele* [78], *Mario Pesaro*[27a]), and *Heinz Gschwend* [83]. Participating in the exploration of the stony path towards the final version **7a** of the *A*/*D* component were

Helmut Boos[27b]), *Ivo Felner* [85], *Fritz Elsinger*[27c]) *and Hanspeter Gribi* [79]. Both imido-ester/enamine condensation steps, namely, the intermolecular coupling of the *A*/*D*- with the *B*/*C* component between rings *C* and *D*, and the the closure of the corrin ring between rings *A* and *B* after complexation with Ni^{II} perchlorate required initiation by a strong base.This requirement is interpreted as reflecting activation of the enamine reaction center through CH deprotonation at C(8) of ring *B* [10]. The structure of the first synthetic corrin complex quickly passed the test of an X-ray structure analysis by *J. D. Dunitz* and *E. F. Meyer* [4][218]. Shortly afterwards, the synthesis of the corresponding dicyano-Co^{III}-corrinate complex was also accomplished [5][6]. In the wake of this achievement, a symposium at the Royal Society in London '*Discussion on Recent Experiments on the Chemistry of Corrins*' was organized by *Dorothy Hodgkin*[26]). Prominent guest present at the Symposium was *Robert Burns Woodward*.

entsprechend robusten, planar-quadratischen oder octahedralen Prä-corrinat-Komplex unter Ausnützung eines starken Templat-Effekts erreicht werden.

Nach diesem (*A*/*D* + *B*/*C*)-Konzept gelang im Frühjahr 1964 der Mitarbeitergruppe *E. Bertele*, *R. Scheffold*, *M. Pesaro* und *H. Gschwend* [3–6] erstmals die Synthese eines Corrin-Komplexes, des *rac*-Ni^{II}-15-cyano-l,7,7,12,12,19-pentamethylcorrinat-chlorids **8zn** (R = H, R^1 = Me, M = Ni^{II}[19]); vgl. *Fig. 8*). Die beiden hemicorrinoiden Komponenten **7b** und **8n** waren durch zwei konsekutive, in beiden Fällen durch starke Basen ausgelöste Imidoester–Enamin-Kondensationen vereinigt worden, im ersten Schritt *inter*molekular zwischen den Ringen *C* und *D*, und abschliessend *intra*molekular zwischen den Ringen *A* und *B* innerhalb des robusten *A*/*B*-secocorrinoiden Ni^{II}-Komplexes **8yn**. Die Struktur **8zn** (M = Ni^+) des synthetischen Corrin-Komplexes erfuhr unmittelbar ihre Bestätigung durch eine *Röntgen*-Strukturanalyse von *Dunitz* und *Meyer* [4][218]. Kurz darauf gelang auch die Synthese des entsprechenden Dicyano-Co^{III}-corrin Komplexes **8zn** (M = $Co(CN)_2$) [6]. Aus diesem Anlass organisierte *Dorothy Hodgkin* ein der Chemie der Corrine gewidmetes Symposium an der Royal Society in London[26]).

2.2. *Corrin-Synthese* via *(*A → B*)-Ringschluss: Synthese von Ni^{II}- und Dicyano-Co^{III}-Komplexen des* rac*-19,7,7,12,12-Pentamethylcorrins*[19]*), des* rac*-7,7,12,12-Tetramethylcorrins, und des* rac*-1,2,2,7,7,12,12-Heptamethylcorrins.*

Im Zeitraum 1960–1967 waren nach dem (*A*/*D* + *B*/*C*)-Konzept die Synthesen der Ni^{II}- und Dicyano-Co^{III}-Komplexe von insgesamt drei konstitutionell verschiedenen Corrin-Liganden entwickelt worden. Die drei Synthesen benützten die gleiche *B*/*C*-Komponente **7b** sowie die gleichen Verfahren zu deren Vereinigung mit dem *A*/*D*-Teil; indessen unterschieden sie sich in der Konstitution der *A*/*D*-*Kompo*nenten und den Synthesekonzepten, die zu deren Herstellung führten. Einen Überblick über diese drei

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[26]) 'A Discussion on Recent Experiments on the Chemistry of Corrin', organized by *Dorothy Crowfoot-Hodgkin*, F. R. S.; Discussion held June 4, 1964; *cf. Proc. Roy. Soc. A* **1965**, *288*, 293–360.

[27]) a) *Mario Pesaro*, Postdoktoratsarbeiten, 1960–1966; b) *Helmut Boos*, Doktoratsarbeiten, 1960–1961, c) *Fritz Elsinger,* Postdoktoratsarbeiten, 1960–1962, d) *A. Peter Johnson*, Postdoktoratsarbeiten, 1966–1967, e) Fritz Karrer, Postdoktoratsarbeiten, 1968–1969.

Corrin-Synthesen gibt die *Fig. 8*; gleichzeitig orientiert diese über die wichtigsten Inhalte der *Teile II–IV* dieser Publikationsreihe.

Der rechts liegende Teil der *Fig. 8* zeigt den ursprünglich entwickelten Syntheseweg zum bicyclischen Lactam **6f** und der gemeinsamen *B*/*C*-Komponente **7b**. Die Herstellung dieses wichtigen Zwischenprodukts aus dem monocyclischen Ringvorläufer **6e** war erstmals *Rolf Scheffold* [77] durch *N*-Acylierung des Methyliden-lactams **6e** mit *β*,*β*-Dimethyllävulinsäure-chlorid und anschliessender thermischer oder photochemischer (N → C)-Acyl-Umlagerung gelungen (vgl. **6e** → **8b** → **8c**); später hat dann *Pius Wehrli* [86] das Verfahren durch eine direkte thermische *C*-Acylierung von **6e** mit dem Enol-lacton **8a** präparativ vereinfachen können. Das hemicorrinoide bicyclische Lactam **6f** hat sich in der Folge als ein äusserst versatiler Synthesebaustein herausgestellt; es kam in unseren sämtlichen späteren Synthesen auf dem Gebiete der Modell-Corrine sowie corrinoiden Hydrophyrine zum Zuge.

Das in *Fig. 8* gezeigte und im *Teil II* dieser Reihe ausführlich beschriebene Herstellungsverfahren für **6f** blieb bis 1967 im Gebrauch. Dann wurde es abgelöst durch das im Zusammenhang mit der Synthese der *B*/*C*-Komponente für die Synthese des Vitamins B_{12} entwickelten Lactam–Enamid-Kondensationsverfahren *via* 'Sulfid-Kontraktion' (s. u.), das einen bedeutend einfacheren (und auch zuverlässigeren) Weg zur Gewinnung dieses zentralen Zwischenprodukts aller Corrin-Modellsynthesen ermöglichte [14]; dieser Weg zur Herstellung von **6f** durch Verknüpfung der Ringvorläufer *B* und *C* nach dem Sulfid-Kontraktionsverfahren ist (dem zeitlichen Ablauf unserer Arbeiten entsprechend) im Kontext mit der photochemischen Corrin-Synthese im *Teil VI* beschrieben (vgl. auch unten, *Abschn. 3.6*). Im *Teil II* werden hingegen von **6f** nebst den ursprünglich verwendeten Herstellungsmethoden auch einige seiner chemischen Eigenschaften als Vertreter des Strukturtyps eines *N*-Acyl-*N*′-vinylvinamidins, insbesondere auch seine Überführung in die aktivierte Form, d. h. das Imidoester-Derivat **7b** behandelt.

Der links liegende Teil der *Fig. 8* skizziert die Synthesen von drei unterschiedlichen hemicorrinoiden *A*/*D*-Komponenten. Die Reaktionsfolge **8e** → **8n** (R = H, R^1 = Me) war das Endergebnis der Arbeiten, die 1960 der ursprünglichen Zielvorstellung entsprechend in Richtung auf ein Lactam-Derivat mit isomerer Lage der angulären Me-Gruppe begonnen worden waren und dann schliesslich zu der in der ersten Corrin-Synthese verwendeten *A*/*D*-Komponente **8n** (R = H, R^1 = Me) führten. Mehrere Stufen des Aufbaus dieser *A*/*D*-Komponente waren für die damalige Zeit präparativ neuartig: so die in hoher Ausbeute verlaufende, reduktive Spaltung der (C–C)-Bindung **8f** → **8g** in dem aus Isopren und Ethylentetracarbonsäure-tetramethyl-ester erhaltenen *Diels–Alder*-Edukt, sodann die diastereoselektive Addition einer aziridinischen NH-Gruppe an eine (C=C)-Bindung *via* intramolekulare Nachbargruppenbeteiligung einer Imidoester-Funktion bei der Halogenierung dieser (C=C)-Bindung **8h** → **8i**, ferner die regio- und diastereoselektive (offenbar als S_N2-Reaktion ablaufende) Öffnung des Aziridin-Rings von **8i** durch Azid-Ionen zu **8k**, nicht zuletzt auch die anhand der Konfigurationsbestimmung von **8i** demonstrierte Methode eines Konfigurationsnachweises für 2,3-disubstituierte Aziridine mittels einer konfigurationserhaltenden nitrosierenden Rückbildung der entsprechenden (C=C)-Bindung [85], sowie schliesslich die in unseren späteren Arbeiten öfters verwendete Methodik der Umwandlung einer Lactam-Gruppierung in ein exocyclisches *β* -Cyano-enamin-

System. Im *Teil II* dieser Publikationsreihe werden diese Reaktionsstufen eingehend erläutert.

Lehrreich wie die Reaktionsfolge **8e** → **8n** für unsere späteren Arbeiten auch gewesen sein mag, für die Bereitstellung grösserer Mengen einer *A*/*D*-Komponente für einen Nachschub an synthetischen Corrinen war sie zu umständlich. Um 1964/66 hatten wir deshalb das Problem der Herstellung leichter zugänglicher *A*/*D*-Komponenten bearbeitet, wobei wir uns diesmal – im Gegensatz zum ersterarbeiteten Syntheseweg – von der Frage nach einer möglichen Übertragbarkeit der Ergebnisse auf das B_{12}-Projekt unbeeinflusst hielten. Das Resultat war der kurze und anscheinend sehr einfache Weg **8o** → **8q** → **8r** → **8s** zur nichtmethylierten *A*/*D*-Komponente **8s** ($R = R^1 = H$) ausgehend von Pyrrolidin-2-on. Durchgesetzt hat sich dieser Weg jedoch nicht: einerseits deshalb, weil seine Schlüsselstufe, die durch Photosensibilisierung ausgelöste Dehydro-Dimerisierung des Pyrrolidin-2-ons (erwartungsgemäss) diastereounselektiv verlief, und die präparative Trennung der diastereoisomeren Dilactame **8p** durch fraktionierende Kristallisation schwierig war, andererseits vor allem auch deswegen, weil sich wenig später in der Reaktionssequenz **6e** → **8t** → **8u** → **8v** → **8w** → **8x** ein präparativer einfach zu durchlaufender Zugang zu der am Ring *A* dreifach methylierten *A*/*D*-Komponente **8x** ($R = CH_3/R^1 = H$) aufgetan hatte [8]. Die Arbeit an der Synthese dieser dritten *A*/*D*-Komponente war durch eine von *Alexander Wick* bei Modellversuchen zum '*B*/*C*-Problem' des B_{12}-Projekts gemachte Beobachtung ausgelöst worden, wonach das K-Salz des Methyliden-lactams **6e** mit $MeNO_2$ zu **8t** reagiert. Zwar verlief die nachfolgende Reaktionsstufe **8t** → **8u** diastereounselektiv, doch erwies sich die Diastereoisomeren-Trennung bei der Station Dilactam **8v** als äusserst einfach, und die von diesem Lactam ausgehenden weiteren Stufen zur *A*/*D*-Komponente **8x** ($R = Me$, $R^1 = H$) verliefen hochgradig regioselektiv.

Der mittlere Teil der *Fig. 8* betrifft die gemeinsame Schlussphase der drei nach dem (*A*/*D* + *B*/*C*)-Konzept realisierten Corrinat-Synthesen, d.h. die Vereinigung der aktivierten *B*/*C*-Komponente **7b** mit je einer der drei *A*/*D*-Komponenten **8n**, **8s**, und **8x** (für R,R^1 vgl. Legende). In der Pentamethyl-Reihe war 1964 im Gefolge der Synthese des Ni^{II}-corrinats **8zn** ($M^+ = Ni^+$) und – nach Überwindung einiger 'Co-spezifischer' Schwierigkeiten – auch die Synthese des entsprechenden Dicyano-Co^{III}-5-cyanopentamethyl-corrinats **8zn** ($M = (CN)_2Co$) gelungen [5][6]. Analog sind später auch die entsprechenden Co-Komplexe der Tetra- und Heptamethyl-Reihe bereitet worden [7][8]. Noch später wurde in der Heptamethyl-Reihe auch noch der entsprechende Pd^{II}-Corrin-Komplex hergestellt, dies zuhanden eines chemischen Beweises für den strukturellen Verlauf der photochemischen (*A*/*D*-Secocorrin → Corrin)-Cycloisomerisierung (s.u.). Hilfreich für die spektroskopische 'Identifikation' der synthetischen Co^{III}-Corrinate war der um jene Zeit von *Reinhart Keese* [199] erstmals kristallin isolierte, durch Methanolyse von Vitamin B_{12} gewonnene Cobyrinsäure-heptamethylester **1d**, eine Verbindung, die in der Folge sowohl im Zusammenhang mit der Bearbeitung der chemischen als auch biologischen Synthese von Vitamin B_{12} unter dem Namen 'Cobester' bekannt und wichtig wurde. Im Übrigen haben *Shaffner* und *Lenhert* [219] um 1968 die Struktur des synthetischen Dicyano-Co^{III}-15-cyano-l,2,2,7,7,12,12-heptamethylcorrinats **8zx** ($M = Co(CN)_2$) durch *Röntgen*-Strukturanalyse festgelegt, und damit auch eine formal noch übrig gebliebene Ungewissheit beseitigt, nämlich die

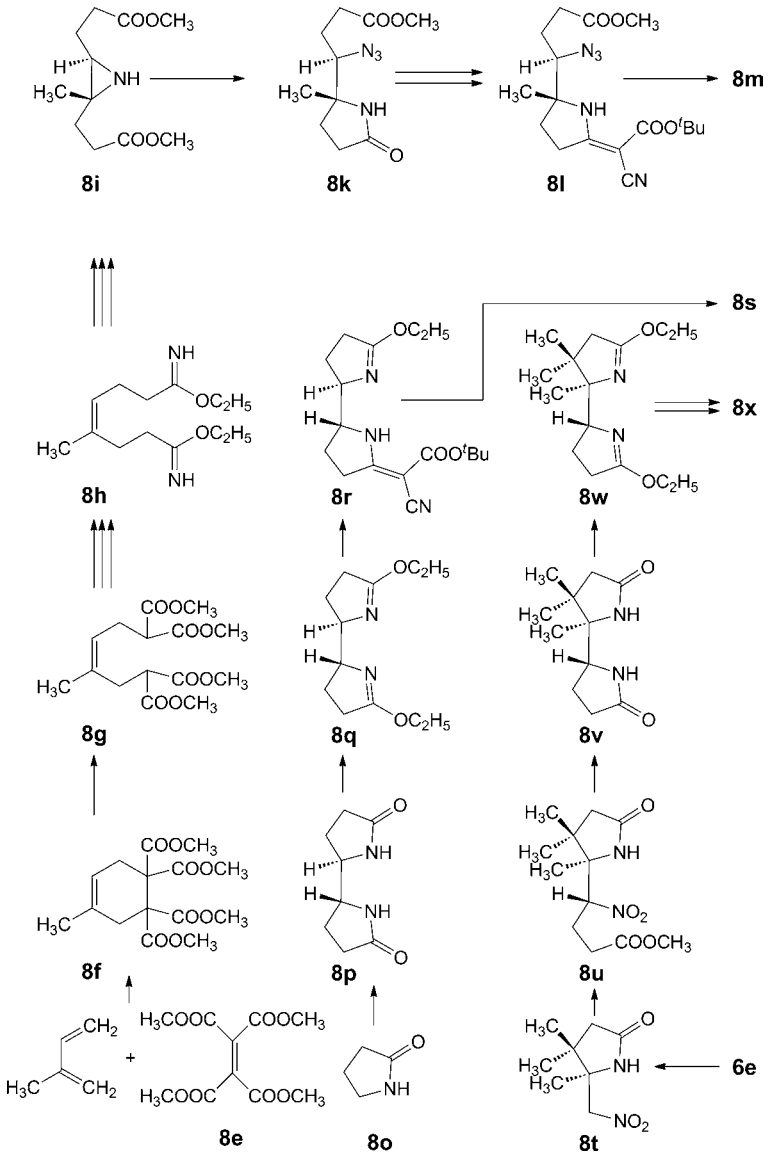
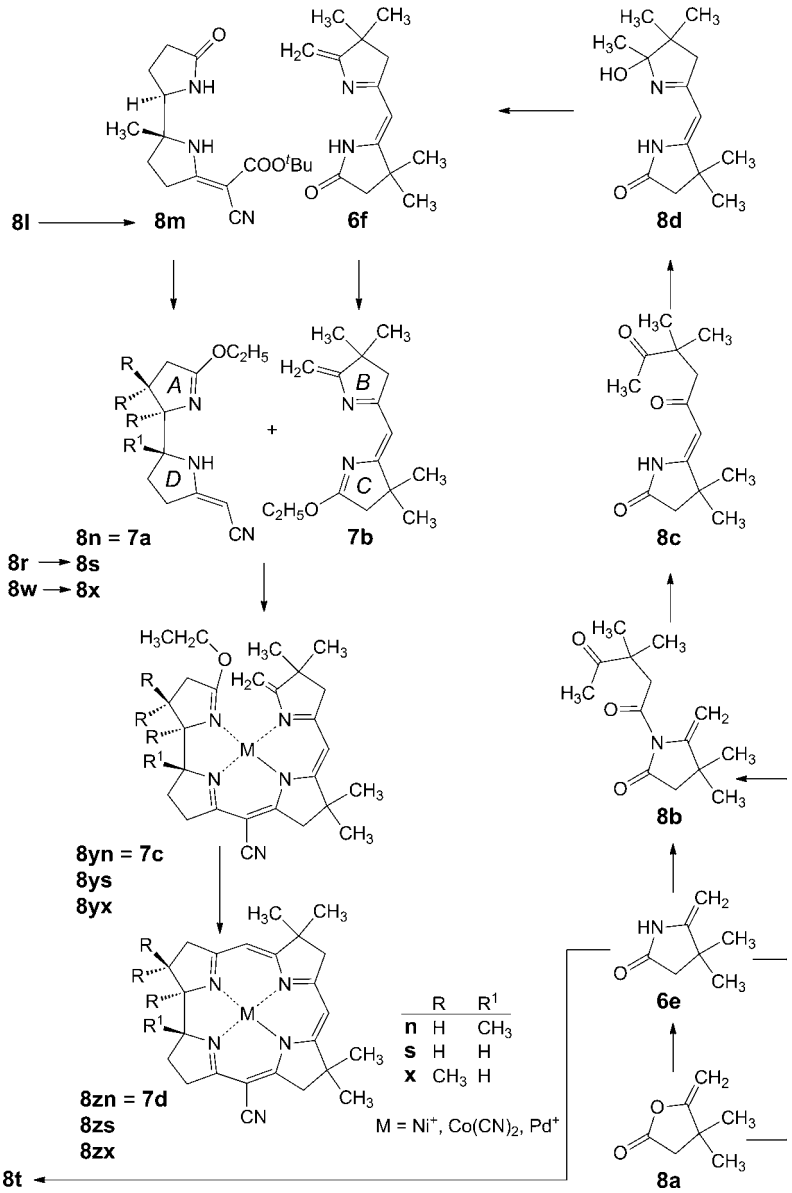


Fig. 8. Within the period 1960 – 1967, three different corrin ligands were synthesized, all by the *A*/*D* + *B*/*C* strategy, and all by using the same *B*/*C* component, but *A*/*D* components that differ from each other by the number of peripheral Me groups. This *Figure* outlines these syntheses in a abbreviated form; however, the reaction conditions of all steps are given below. The formulae on the *Figure*'s right-hand side show the pathway by which the *B*/*C* component was originally constructed, those on the left-hand side, the three synthetic routes leading to the three different *A*/*D* components, and the formula sequence in between the final two steps of all three



corrin syntheses, including the strategy-defining, final *A*/*B*-secocorrin → corrin cyclization. The three parts of the *Figure* correspond to the main topics of *Parts II*, *III*, and *IV* of the publication series.

Reaction conditions [4][6–8]: *Preparation of* B/C *component* **7b** [4][77][86]: **8a** → **6e**: NH_3/130°; 96%; **6e** → **8b**: ^{t}BuOK in MeCN, 3,3-dimethyl-4-oxopentanoyl chloride; 81%; **8b** → **8c**: *hν* (254 nm) in cyclohexane; 45%; or 290°; 30%; **8a** + **6e** → **8c**: 320°, without solvent; 25–50%; **8c** → **8d**: NH_3 in MeOH; 80%; **8d** → **6f**: ^{t}BuOK in ^{t}BuOH; 85%; **6f** → **7b**: $Et_3O^+ \cdot BF_4^-$ in CH_2Cl_2; 86%.

Preparation of A/D *component* **8n** (R = H, R^1 = Me) [4][79][85]: **8e** → **8f**: 190°; 98%; **8f** → **8g**: Na in NH_3 / THF, −70° → r.t.; 89%; **8g** → **8h**: a) KOH/MeOH, r.t.; HCl; Δ/reflux in *sym*-collidine; 83% dimethyl ester; b) NH_3/EtOH, 155°; 84%; c) $Et_3O^+ \cdot BF_4^-$ in CH_2Cl_2, r.t.; 86%; **8h** → **8i**: a) Br_2/CH_2Cl_2 → 5N K_2CO_3/0°; b) H_2SO_4/H_2O, r.t.; c) Na_2CO_3, r.t.; 75%; **8i** → **8k**: NaN_3/H_2SO_4/MeOH, r.t.; 56%; **8k** → **8l**: a) $Et_3O^+ \cdot BF_4^-$ in CH_2Cl_2 → 5N K_2CO_3, 0°; b) $NCCH_2COO^tBu$, Et_3N; 86%; **8l** → **8m**: a) H_2/Pd/EtOH; b) Δ/reflux in anisole; 92%; **8m** → **8n** (= **7a**): CF_3COOH, r.t. → 30°; → $Et_3O^+ \cdot BF_4^-$ in CH_2Cl_2, → 5N K_2CO_3, 0°; 66%.

Preparation of A/D *component* **8s** (R = H, R^1 = H) [7][85]: **8o** → **8p**: *hν* (UV/Hg) in acetone, N_2, r.t.; 12% of diastereoisomers (1:1) → fractional crystallization; **8p** → **8q**: $Et_3O^+ \cdot BF_4^-$ in CH_2Cl_2/reflux, → EtONa in EtOH, 0°; 68%; **8q** → **8r**: $NCCH_2COO^tBu$, Et_3N, r.t.; 89%; **8r** → **8s**: CF_3COOH, r.t.; 74%.

Preparation of A/D *component* **8x** (R = Me, R^1 = H) [8][85]: **6e** → **8t**: in $MeNO_2$, ^{t}BuOK, 60°; 84%; **8t** → **8u**: Methyl acrylate, '*Triton B*' in MeOH, r.t.; 78% of diastereoisomers (*ca.* 1:1); **8u** → **8v**: *Raney*-Ni/H_2/300 atm.; isomer **8v** crystallizes from CH_2Cl_2; 80%; **8v** → **8w**: $Et_3O^+ \cdot BF_4^-$ in CH_2Cl_2, r.t., → 5N K_2CO_3, 0°; 82%; **8w** → **8x**: a) $NCCH_2COO^tBu$, Et_3N, N_2, 40°, 135 h; 81%; b) CF_3COOH, r.t., crystallization from CH_2Cl_2/hexane; 74–87%.

Synthesis of corrin complexes **8zn** (R = H, R^1 = Me)*,* **8zs** (R = H, R^1 = H)*, and* **8zx** (R = Me, R^1 = H) [4][6–8][83][88][95][90]: **8zn** (R = H, R^1 = Me): **8n** + **7b** → **8yn** (M = Na): **8n** in diglyme + EtONa/EtOH + **7b** in diglyme, N_2, 40°; 70%; **8yn** (M = Na) → **8yn** (M = Ni^+): Ni^{2+} $(H_2O)_6 \cdot (ClO_4^-)_2$ in MeCN; 80%; **8yn** (M = Na) → **8yn** (M = $Co(CN)_2$): Co^{2+} $(H_2O)_6 \cdot (ClO_4^-)_2/H_2O$, N_2, → KCN/air; 58%; **8yn** (M = Ni^+) → **8zn** (M = Ni^+): ^{t}BuOK/^{t}BuOH, reflux, → $HClO_4$; 88%; **8yn** (M = $Co(CN)_2$) → **8zn** (M = $Co(CN)_2$): ^{t}BuOK/^{t}BuOH, N_2, r.t., → KCN, H_2O, air; 93%; **8zs** (R = H, R^1 = H): **8s** + **7b** → **8ys** (M = Na): **8s** in diglyme + EtONa/EtOH + **7b** in diglyme, N_2, 40°; 51%; **8ys** (M = Na) → **8ys** (M = $Co(CN)_2$): Co^{2+} $(DMF)_6 \cdot (ClO_4^-)_2$/EtOH, N_2; KCN, air; 56%; **8ys** (M = $Co(CN)_2$) → **8zs** (M = $Co(CN)_2$): **8ys** in pyridine, ^{t}BuOK, ^{t}BuOH, N_2, r.t., → KCN, H_2O, air; *ca.* 90%; **8zx** (R = CH_3, R^1 = H): **8x** + **7b** → **8yx** (M = Na): **8x** in diglyme + EtONa, EtOH + **7b** in diglyme, N_2, 60°; 70%; **8yx** (M = Na) → **8yx** (M = Ni^+): **8yx** in MeCN + Ni^{2+} $(H_2O)_6 \cdot (ClO_4^-)_2$ in MeCN, r.t.; 70%; **8yx** (M = Na) → **8yx** (M = Pd^+): **8yx** in EtOH + $Pd(CH_3COO)_2$, r.t.; 52%; **8yx** (M = Na) → **8yx** (M = $Co(CN)_2$): **8yx** + Co^{2+} $(H_2O)_6 \cdot 2Cl^-$, EtOH, N_2, → KCN, air; 67%; **8yx** (M = Ni^+) → **8zx** (Me = Ni^+): ^{t}BuOK, ^{t}BuOH, N_2, 80°, → $HClO_4$, H_2O; 86%; **8yx** (M = Pd^+) → **8zx** (M = Pd^+): ^{t}BuOK, ^{t}BuOH, 140° in evacuated tube, → $HClO_4$, H_2O; 83%: **8yx** (M = $Co(CN)_2$) → **8zx** (M = $Co(CN)_2$): ^{t}BuOK, ^{t}BuOH, DMF, N_2, 50°, → KCN, H_2O, → air; 65%.

The method of preparing the bicyclic lactam precursor **6f** of the *B*/*C* component **7b** shown on the *Figure*'s right-hand side depended on the *C*-alkylation of the monocyclic ene-lactam **6e** *via* either *N*-alkylation to **8b**, followed by either thermal or photochemical N → C rearrangement to give **8c**, or direct formation of the latter (presumably proceeding *via* **8b**) by thermal coupling of ene-lactone **8a** with ene-lactam **6e**. Both variants proceeded with less than satisfactory yields; this was to be temporarily accepted in view of our failure to combine **6e** with itself by an imido ester/enamide condensation. The sequence **6e** → **8c** → **8d** → **6f** remained as a source of bicyclic lactam **6f** until 1967, when it was replaced by the far more efficient

coupling of **6e** with itself by the sulfide-contraction method (see *Fig. 18*). An important step in the synthesis of the final *B*/*C* component **7b** is the delicate, but reliably successful activation of the lactam group of **6f** by *O*-alkylation with *Meerwein*'s $Et_3O^+ \cdot BF_4^-$.

The left-hand side of the *Figure* illustrates the access to the three different *A*/*D* components **8n** (= **7a**), **8s**, and **8x**. The twelve-steps reaction **8e** → **8n** (R = H, R^1 = Me) is the one that was realized first and led in 1964 to the corrin complexes **8zn** (= **7d**) (M = Ni^+ and $(CN)_2Co$). A number of steps in this sequence were (for that time) novel transformations: first and above all, the reductive cleavage **8f** → **8g** of the C–C bond in the *Diels–Alder* adduct **8f** as a general diastereoselective access to (*Z*)-olefinic bonds such as that in the tetraester **8g**, second, the diastereoselective addition **8h** → **8i** of an aziridinic NH group to that C=C bond *via* a electrophilic halogenation, regioselectively assisted by an intramolecularly participating imido-ester NH group, third, the regio- as well as diasteroselective opening of that aziridine ring by an S_N2-process with azide anion to give **8k**, and forth, the conversion of a lactam group such as the one in **8k** to a corresponding enamine–nitrile grouping *via* activation of the lactam carbonyl with *Meerwein* salt, imido-ester condensation with *tert*-butyl 2-cyanoacetate, and selective hydrolysis accompanied by decarboxylation (**8k** → **8l** → **8m** → **8n** (= **7a**)). Another novelty (for that time) was the chemical establishment of the configuration of the aziridine **8i** by converting it back to the olefin by nitrosation, a reaction that was shown in model studies to proceed with retention of configuration (*cf.* [85] and *Part III* of this series).

As much as we had learned in developing the synthesis of this first *A*/*D* component **7a** (= **8n**), the synthesis was too complicated for what we had in mind beside the pursuit of a B_{12}-model study, namely, a systematic investigation of the chemistry of synthetic corrins. Therefore, in 1965/1966, an effort was made to develop simpler pathways to *A*/*D* components and, among them, to the simplest of all, the one without any angular Me group. A synthesis of the simplest *A*/*D* component **8s** (R = R_1 = H) could in fact be realized *via* the symmetrical *trans*-dilactam **8p**, found to be accessible by a sensitized photochemical bis-dehydro-dimerization of pyrrolidin-2-one **8o**. However, the pathway **8p** → **8q** → **8r** → **8s** again turned out to be unsuitable for the preparation of larger amounts of an *A*/*D* component, because – even though the procedure for the photochemical step **8o** → **8p** in acetone as the solvent was very simple indeed and could be carried out with large amounts of inexpensive starting material – it proceeded in low yield only, affording two diastereoisomeric dilactams in the ratio of 1:1 which had to be separated by a most cumbersome fractional crystallization. Assignment of configuration was achieved *via trans*-imido-esterification of bis(imido ester) **8q** with (−)-menthol.

In the meantime, the (unforseen) observation that the K salt of ene-lactam **6e** in $MeNO_2$ in the presence of a base reacts with the solvent to give the adduct **8t**, initiated the development of the reaction sequence **8t** → **8x** which became the third synthesis of an *A*/*D* component. It rendered obsolete both syntheses discussed thus far. *Michael* addition of **8t** to methyl acrylate gave the (expected) mixture of two diastereoisomeric adducts which were not separated, but converted to the corresponding dilactams, from the mixture of which the desired diastereoisomer **8v** could be easily obtained by crystallization. The isomer in the mother liquour could be

equilibrated back to the mixture of diastereoisomers. One of the two imido-ester groups in the bis(imido esters) **8w** being sterically hindered, the follow-up imido-ester condensation to eventually give **8x** proceeded with high regioselectivity.

The formulae in the central part of *Fig. 8* outline the two final steps in the syntheses of Ni^{II} and dicyano-Co^{III}-15-cyanocorrin complexes differing only in the number of peripheral Me groups. The two intrinsically delicate steps eventually proceeded reliably and in remarkably high yield. The decisive result of an extensive exploration of the conditions for the ring closure **8yn** → **8zn** was a strict requirement of a strong base for this final step (activation of the enamine reaction center through deprotonation at C(8) of ring *B*).

The intermediates and products encountered in these three corrin syntheses were all rigorously characterized by UV/VIS, IR, and ^{1}H-NMR spectroscopy, most of them also by elemental analysis, some of them by mass spectrometry [220], and a few of them by X-ray-analysis. Of special significance was the early X-ray structure analysis of the target complex of the very first corrin synthesis, *i.e.*, **8zn**, M = Ni, by *Meyers* and *Dunitz* [218][4]. The X-ray structure analysis of the dicyano-Co^{III}-complex **8zx** in the *hepta*methyl series carried out later by *Galen Lenhert* and *Shaffner* [219] not only verified the overall structure of this 15-cyano-heptamethylcorrinate, but also provided the final confirmation of the relative configuration of the *A*/*D* component **8x**.

relative Konfiguration der trimethylierten *A*/*D*-Komponente **8x** (R = Me, R^1 = H) der Heptamethylcorrin-Reihe.

Ab Ende 1966 konzentrierten sich unsere Arbeiten über synthetische Corrine nahezu ausschliesslich auf die weitaus am einfachsten und effizientesten zugängliche Heptamethyl-Reihe, in welcher Corrin-Derivate durch Vereinigung der trimethylierten *A*/*D*-Komponente **8x** mit der für alle drei Reihen identischen *B*/*C*-Komponente **7b** entstehen. Abgesehen von seiner leichten Zugänglichkeit, erschien dieser Weg vor allem auch in konzeptueller Hinsicht attraktiv: das En-lactam **6e** diente nunmehr nicht nur als Vorläufer des Ringes *C*, sondern ebenso als solcher des Ringes *A*. *Fig. 9* illustriert den (Edukt/Zwischenprodukt/Produkt)-Zusammenhang in der Heptamethyl-Reihe **9a** → (**9b**) → **9c**; die Corrin-Synthese in dieser Reihe war von allen drei nach der (*A*/*D* + *B*/*C*)-Strategie realisierten Varianten die präparativ effizienteste und dementsprechend bis zum Zeitpunkt ihrer Ablösung durch die photochemische Synthese durch (*A*/*D*-Secocorrin → Corrin)-Cycloisomerisierung im Jahre 1968 (s. u.) in unserem Laboratorium die bevorzugte Herstellung von Corrin-Komplexen.

Fig. 9 stellt zudem noch zwei wichtige Befunde dar: zum einen die Tatsache, wonach nicht nur in entsprechenden Ni^{II}-corrinaten, sondern auch in Dicyano-Co^{III}-corrinaten des Typs **9c** die chromophorgebundene CN-Gruppe in der *meso*-Stellung, d. h. C(15), auf hydrolytisch-decarboxylativem Wege entfernt werden kann (vgl. **9c** → **9d**). Diese CN-Gruppe hatte für das Gelingen des (*A*/*D* + *B*/*C*)-Corrin-Synthesekonzepts eine wichtige Hilfsfunktion zu erfüllen; seine abschließende Entfernbarkeit war u. a. eine Voraussetzung für die weiter unten beschriebenen B_{12}-relevanten Modellstudien zur Einführung von Me-Gruppen in die *meso*-Stellungen C(5) und C(15) des Corrin-Chromophors.

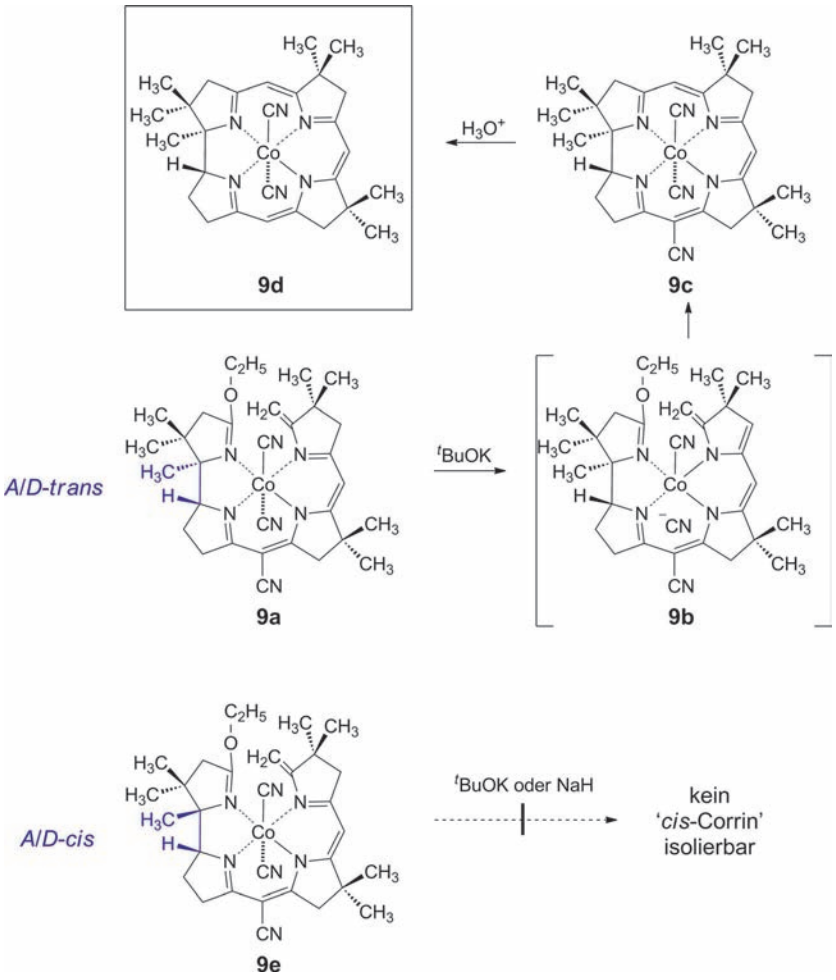


Fig. 9. The reaction sequence **6e** → **8zx** in the heptamethyl series was the by far simplest and most efficient of all our earlier corrin syntheses. It, therefore, served in our laboratory as the main source of synthetic corrin derivatives until 1968, the year of the breakthrough to the corrin synthesis *via* *A*/*D*-secocorrin → corrin cyclo-isomerization (see *Fig. 22*). Not only experimentally, but also conceptually did the reaction sequence have a special appeal, because, in this synthesis, ene-lactam **6e** was to serve as the building block not only for ring *C* and (indirectly) ring *B*, but also for ring *A*. Even though the three Me groups present in ring *A* exert a retarding effect on the final corrin ring closure by *A* → *B* imido-ester/enamine condensation, the dicyano-Co^{III}-*A*/*B*-secocorrinate **9a** cyclized to the corresponding corrinate **9c** at slightly elevated temperature in good yield. In all of these *A* → *B* cyclizations, the use of a strong base, such as ^{t}BuOK in solvents such as DMF containing small amounts of ^{t}BuOH, was found to be a strict requirement for deprotonation of the peripheral CH_2

group in ring *B* to form the activated enamine **9b** as the ring-closing intermediate. Remarkably enough, in this and all previously prepared corrin complexes containing a CN substituent at C(15) of the corrin chromophore, it was possible to remove this substituent in high yield by vigorous acid-catalyzed hydrolysis and concurrent decarboxylation without destruction of the corrin chromophore. Constitutionally, the dicyano-Co^{III}-1,2,2,7,7,12,12-heptamethylcorrinate **9d** obtained from **9c** in this way resembled 'cobester' (*cf. Fig. 1*) more closely than any of the previously synthesized model corrins.

The *Michael* additions **8t** → **8u** in the synthesis of the *A*/*D* component of the heptamethyl series resulted in, as already mentioned, a mixture of two diastereoisomeric adducts (*cf. Fig. 8*). It was possible, therefore, to get hold of the diastereoisomer of the dilactam **8v** and, from there, of the dicyano-Co^{III}-*A*/*B*-secocorrinate **9e**, which differs from **9a** by a *cis*-configuration at the direct junction of rings *A* and *D*. The complex was specifically prepared in order to check experimentally whether corrin diastereoisomers containing a *cis*-junction between rings *A* and *D* would also be accessible. Not unexpectedly, under conditions where the *trans*-secocorrinate **9a** cylized to corrinate **9c**, the *cis*-isomer **9e** resisted cyclization even under far more severe conditions; in such experiments the free ligand was recovered and/or decomposition was observed.

Reaction conditions [8][88][90][96]: **9a** → (**9b**) → **9c**: ^{t}BuOK, ^{t}BuOH, DMF, N_2, 50°; 65%; **9c** → **9d**: 0.1N HCl, N_2, 230° in closed tube; workup with KCN; 84%; **9e** → no *cis*-corrin complex [96]: ^{t}BuOK, DMF, 50° or NaH, diglyme, 100°, or ^{t}BuOK, diglyme, 200°.

Der andere Befund betrifft den misslungenen Versuch, Reaktionbedingungen zu finden, unter welchen das in der Heptamethyl-Reihe zugängliche *cis*-Isomere **9e** des Dicyano-Co^{III}-*A*/*D*-secocorrin-Komplexes **9a** zu einem Corrin-Komplex mit *cis*-Verknüpfung der Ringe *A* und *D* hätte cyclisiert werden können. Der Misserfolg bestätigte die auf Modellbetrachtungen sich stützende Annahme, dass ein solches *A*/*D*-*cis*-Diastereoisomer des *A*/*D*-*trans*-Corrin-Komplexes **9c** relativ zu Letzterem hohe Spannung aufweisen müsste.

Unter all den bemerkenswerten Eigenschaften des monocyclischen En-Lactams **6e** war eine der überraschendsten seine nahezu quantitative Dimersierung **6e** → **10a** unter dem Einfluss von Protonen in apolarem Medium (*Fig. 10*). Die hieraus verfügbar gewordenen bicyclische Dilactam-Form einer '*quasi*-*A*/*D*-Komponente' wurde zum Anlass von Arbeiten, die *Heinz Gschwend* [83] über die Synthese *quasi*-corrinoider Komplexe der Octahydro- und Hexahydro-porphyrin Reihe im Zeitraum 1961 – 1964 durchführte (*Fig. 11*). In diesen frühen Arbeiten diente Pd^{II} als Koordinationszentrum, weil dieses Metall-Ion auf Grund seiner bekannt starken Tendenz zu quadratisch-planarer Koordination für den Ringschluss zum Macrocyclus den stärksten Templat-Effekt versprach. Die aus dem Dimeren **10a** rasch und leicht zugängliche *quasi*-corrinoide *A*/*D*-Komponente **11a** erwies sich als wichtige Modellverbindung für die methodische Erarbeitung der damals durchgeführten Endstufen der ersten Corrin-Synthese **8n** + **7b** → **8yn** → **8zn**, und in der Tat waren denn auch die entscheidenden Reaktionsbedingungen der abschliessenden (*A* → *B*)-Cyclisierung **8yn** → **8zn** (R = H,

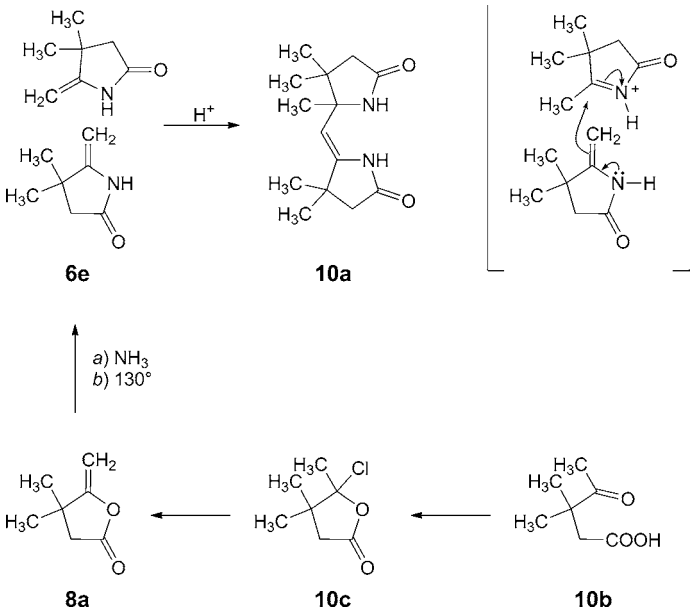


Fig. 10. One of the most remarkable properties of the monocyclic ene-lactam **6e**, first observed by *Scheffold* [77], is its surprisingly smooth and essentially quantitative conversion to the dimer **10a** under the influence of protons in unpolar solvents. With this dimer, an easily accessible *quasi-A*/*D* component became available which offered itself to serve as a model for exploring the access to 'real' *A*/*D* components and their coupling with the *B*/*C* component, this at a time before the first proper *A*/*D* component (compound **8n**≡**7a**) had become available in 1962 [1]. Some of these explorations are outlined in *Fig. 11*. Several syntheses of ene-lactam **6e** were developed for preparing large amounts of this intermediate (*cf. Part II* of this series); one of those syntheses followed the path **10b** → **10c** → **8a** → **6e**.

Reaction conditions [2][6] [77][78][86]: **6e** + **6e** → **10a**: trace of TsOH in CH_2Cl_2, reflux; ≥95%; **10b** → **10c**: $SOCl_2$, 50°; 93%; **10c** → **8a**: Et_3N, benzene, reflux; 63%; **8a** → **6e**: liq. NH_3, *ca.* −40°, reaction product destilled at 124–126°/11 Torr; 96% [86].

R^1 = Me, M = Ni) anhand der Modellcyclisierung **11b** → **11c** mitentwickelt worden [2][6] [13][83].

In dem 1963 auf diese Weise synthetisierten *quasi*-corrinoiden Octahydroporphyrin-Komplex **11c** stammen die Ringe *A*, *C* und *D* alle aus dem gleichen En-Lactam **6e**, welches sich seinerseits aus dem entsprechenden En-Lacton **8a** herleitet und auch Vorläufer des Ringes *B* ist (*Fig. 11*). *Hier liegt der Ursprung des erst viel später zur Reife gelangten Corrin-Synthesekonzepts, in dessen Mittelpunkt das Postulat der Herstellbarkeit aller vier Ringe aus einem gemeinsamen Ringvorläufer stand, und welches dann schliesslich in der photochemischen Variante der Vitamin B_{12}-Synthese seine Verwirklichung fand*. In der Modellreihe war ausgehend von **11a** und **7b** die

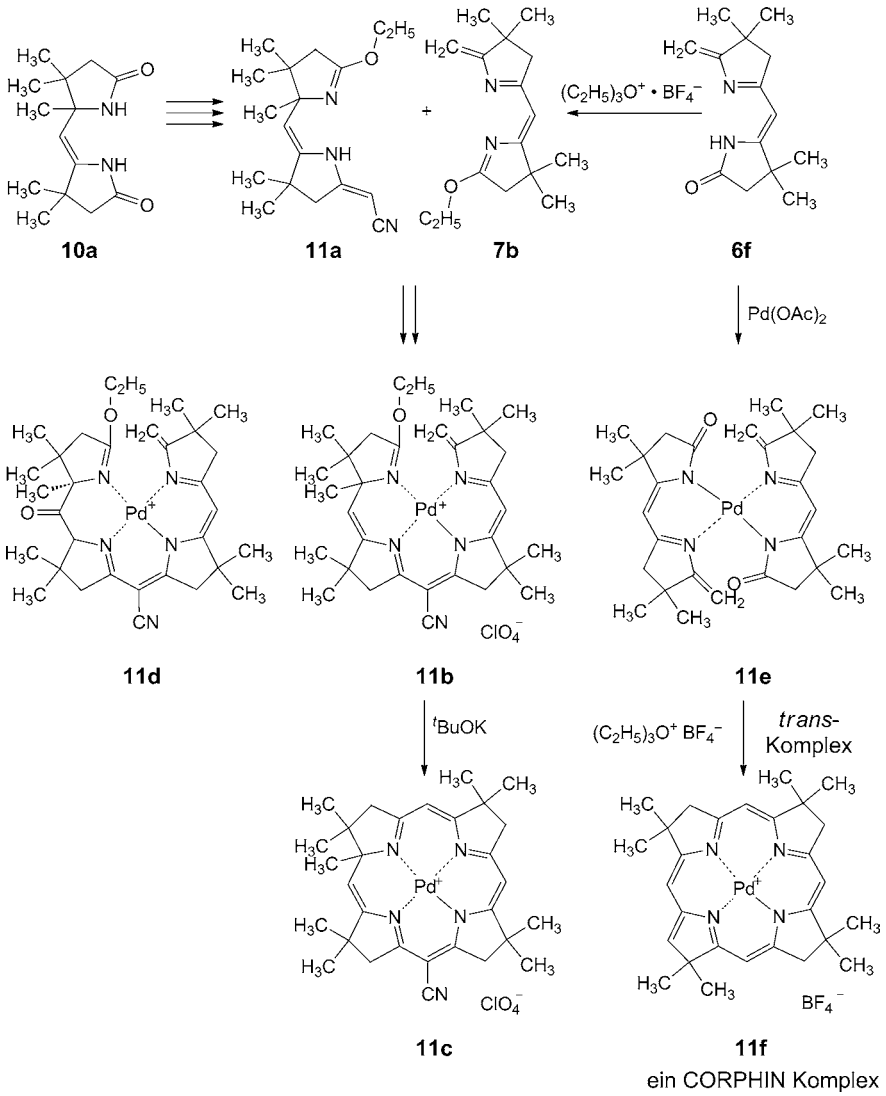


Fig. 11. The explorations starting from the easily accessible dilactam **10a** were carried out in 1961–1963 by *Heinz Gschwend* in his thesis [83]. They were model studies for transformations that would convert a bicyclic dilactam such as **4f** to an *A*/*D* component, couple the latter with an *B*/*C* component, and finally close the macrocyclic ring. These investigations were, so to say, a 'model study within a model study', a search for conditions of C,C-bond forming reactions which were to be part of a model corrin synthesis. The explorations involved the preparation of the *quasi*-*A*/*D* component **11a**, its coupling with the *B*/*C* component **7b**, and the macroring closure by imido-ester/enamine condensation in **11b** to the *quasi*-corrinoid Pd complex **11c**. The information collected in this work was instrumental for the development of the transformations that

eventually led to the 1964 synthesis of a Ni^{II}-corrin complex. In these early studies, Pd was chosen as the coordination center, because this transition-metal ion could be expected to exert the 'strongest possible' template effect in assisting the final ring closure.

An example of how Pd^{II} and Ni^{II} could in fact influence a reaction course quite differently was observed in the synthesis of a *corphin* complex [12][23] by the reaction sequence **6f** → **11e** → **11f**: the twofold cyclization step **11e** → **11f** was successful with Pd^{II}, but not with Ni^{II} as the coordination center. Complexation of **6f** with $Pd(OAc)_2$ gave rise to a mixture of two complexes, both presumed to have a 'planoid' geometry, one of them being the *trans*-isomer **11e**. Complexation with Ni^{II} resulted in the formation of only one complex, presumed to be tetrahedrally coordinated (paramagnetic according to NMR). The bis(diimido ester) of this Ni^{II} complex resisted cyclization under all the conditions tried.

Still another effort to make use of the remarkable dimerization **6e** → **10a** was based on the hypothesis that a Pd^{II}-oxo-*quasi*-*A*/*B*-secocorrin complex **11d** – to be made from **10a** *via* oxidation at its *meso*-position – might open the way to a proper *A*/*B*-secocorrin complex by light-induced decarbonylation, and then, by *A* → *B* cyclization, to a corrin complex. This could eventually be shown to be indeed the case [83] (*cf. Part IV* of this series), but the complexity and the yield of the decarbonylation step were such that the final isolation of the tiny amounts of the corresponding corrin complex did not justify calling the reaction sequence 'a corrin synthesis'. However, the recognition of this 'not quite a synthesis' of a Pd^{II}-nonamethylcorrinate amounted to a mental step forward toward the concept and eventual realization of a 'dream corrin synthesis', one that would start from one single monocyclic intermediate as the precursor of all four peripheral rings of the corrin ligand. *The sustained challenge eventually led to the concept of the corrin synthesis* via *the* A/D-*secocorrin* → *corrin cycloisomerization and found its final fulfillment in the photochemical variant of the vitamin* B_{12} *synthesis.*

Reaction conditions[28]) [2][6] [9][12][23][83][86]: **10a** →→→ **11a**: a) $Et_3O^+ \cdot BF_4^-$, CH_2Cl_2, r.t.; 88% of diimido ester; b) $CNCH_2$–COO^tBu, Et_3N, r.t.; 76% of cyano ester; c) CF_3COOH, r.t.; 95% of cyano acid; d) heating in anisol under reflux; 98% of **11a**; **6f** → **7b**: $Et_3O^+ \cdot BF_4^-$, CH_2Cl_2, reflux; 94%; **11a** + **7b** →→ **11b**: a) ^{t}BuOK, diglyme, r.t.; b) $(NH_4^+)_2 \cdot PdCl_4^-$, DMF; c) $HClO_4$, H_2O; 42%; **11b** → **11c**: ^{t}BuOK, ^{t}BuOH, 80°; 82%; **6f** → **11e**: $NaOCH_3$, $Pd(OAc)_2$, MeCN, r.t.; 26% *cis*-, 24% *trans*-isomer [12]; **11e** → **11f**: $Et_3O^+ \cdot BF_4^-$, CH_2Cl_2, r.t.; 45% [12].

Möglichkeit untersucht worden, auf dem Wege einer photo-induzierten Decarbonylierung des Pd^{II}-Komplexe **11d** und anschliessendem (*A* → *D*)-Ringschluss sozusagen als '*proof of principle*' dieses Ziel zu erreichen [83]; dies ist in der Tat auch gelungen, aber mit Ausbeuten, welche den Begriff 'Synthese' nicht verdienten (vgl. *Teil IV*). Über die Inspiration zur Forderung 'alle Ringe aus einem einzigen Vorläufer' und die zu Beginn erfüllte Funktion eines 'Modell des Modells' bei der Entwicklung der ersten Corrin-Synthese hinaus (vgl. *Teil IV*) präsentiert sich die Synthese des octahydroporphinoiden Pd-Komplexes **11c** als erstes Glied in einer Kette von Arbeiten, die parallel zu den corrinsynthetischen Untersuchungen sich ebenfalls über zwei Jahr-

zehnte hin erstreckten: es war dies die synthetische Erforschung hydroporphinoider Ligand-Systeme im Hinblick auf die Problematik der Corrin-Biosynthese und des Ursprungs des Strukturtyps der natürlichen Corrinoide. Die Kette erstreckt sich vom angulär methylierten *Dihydrocorphin*-Komplex **11c** zum *Corphin*-Komplex **11f** aus dem Jahre 1963 [12][28]), zu entsprechend metallfreien Corphinen [23], bis hin zu der um 1980 erschlossenen (Dihydrocorphinol → Corrin)-Umlagerung [38][39] und anschliessend zu Untersuchungen über Hexahydroporphinoide [40–42][119].

2.3. *Corrin-Synthese* via *(*A → B*)-Ringschluss: Synthese des metallfreien Corrinium-Kations von 15-Cyano-1,2,2,7,7,12,12-heptamethylcorrin und Herstellung von Corrin-Komplexen durch Komplexierung des freien Liganden.*

Im Jahre 1965 hatte *Toohey* [151] im Laboratorium von *Barker* die chemisch und biosynthetisch bedeutsame Entdeckung gemacht, dass gewisse photosynthetisierende Bakterien Co-freie Corrinoide produzieren. Damit war auf dem Gebiete der chemischen Corrin-Synthese die bislang im Hintergrund verbliebene Frage akut geworden: wie synthetisiert man metallfreie Corrine? Der Erfolg der bis dahin erreichten Methodik des (*A* → *B*)-Ringschlusses *via* Imidoester–Enamin-Kondensation war auf die Assistenz von Übergangsmetall-Ionen wie Ni^{II}, Co^{III}, Pd^{II} beschränkt, d.h. auf Übergangsmetall-Ionen, die mit *A*/*B*-secocorrinoiden Ligandsystemen Komplexe bilden die genügend robust sind, um die stark basischen Bedingungen der abschliessenden (*A* → *B*)-Imidoester–Enamin-Kondensation zu überstehen, nach erfolgtem Ringschluss jedoch nicht wieder aus dem Corrin-Ligandsystem entfernt werden können. Um diese Synthese von Corrin-Übergangsmetall-Komplexen zu einer solchen von metallfreien Corrinen auszuweiten, müsste der abschliessende (*A* → *B*)-Ringschluss innerhalb nicht-robuster *A*/*B*-secocorrinoider Komplexe von Metall-Ionen wie z.B. Zn^{II} möglich sein. Solche Versuche erwiesen sich jedoch als erfolglos. Es traf sich nun aber, dass im Laufe des Jahres 1966 in unserem Laboratorium im Zuge des Aufbaus der ETH-Komponente der Harvard/ETH-B_{12}-Synthese die Methodik der Thiolactam/Enamid-C,C-Ringverknüpfung durch Sulfid-Kontraktion *via* oxidative Kupplung entwickelt worden war (Näheres darüber im *Abschn. 2.5*). Durch die in *Fig. 12* skizzierte Übertragung dieses Ringverknüpfungsverfahrens auf das (*A* → *B*)-Ringschluss-Problem in der Heptamethyl-Reihe verwirklichte *Albert Fischli* [9][88] 1967 die Synthese eines Zn^{II}-corrinats **12d** und damit (durch azidolytische Dekomplexierung) erstmals die Synthese eines metallfreien Corrinium-Salzes **12e**. Dessen Struktur (als Chlorid) wurde im *Hodgkin*'schen Laboratorium alsbald *Röntgen*-strukturanalytisch bestätigt [221] (vgl. auch [17]).

Die bezüglich der Wahl von Reagentien und Reaktionsmedien recht komplexe Reaktionsfolge der (*A* → *B*)-Cyclisierung *via* Sulfid-Kontraktion **8yx** → **12a** → (**12b**) → **12c** → **12d** → **12e** ist in der Folge von *Hans-Ueli Blaser* [95] in der Heptamethyl-Modellreihe und dann vor allem von *Peter Schneider* [97] im Rahmen des Vitamin B_{12}-Projekts an dem (an der Ring-*D*-Carboxy-Funktion noch undifferenzierten) 5,15-

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[28]) Bei dieser ersten Synthese eines *Corphin*-Komplexes **11f** durch *A. Peter Johnson*[26d]) und *Pius Wehrli* [12][86] war die Verwendung von Pd^{II} als Koordinationszentrum wichtig. Mit Pd^{II} bildete Lactam **6f** zwei diastereoisomere quadratisch-planare Komplexe **11e** (*cis* und *trans*), wobei nur der *trans*-Komplex die Umwandlung **11e** → **11f** einging. Der entsprechende Ni^{II}-Komplex war tetrahedral (paramagnetisch!) und zeigte keine Reaktion des Typs **11e** → **11f** [12].

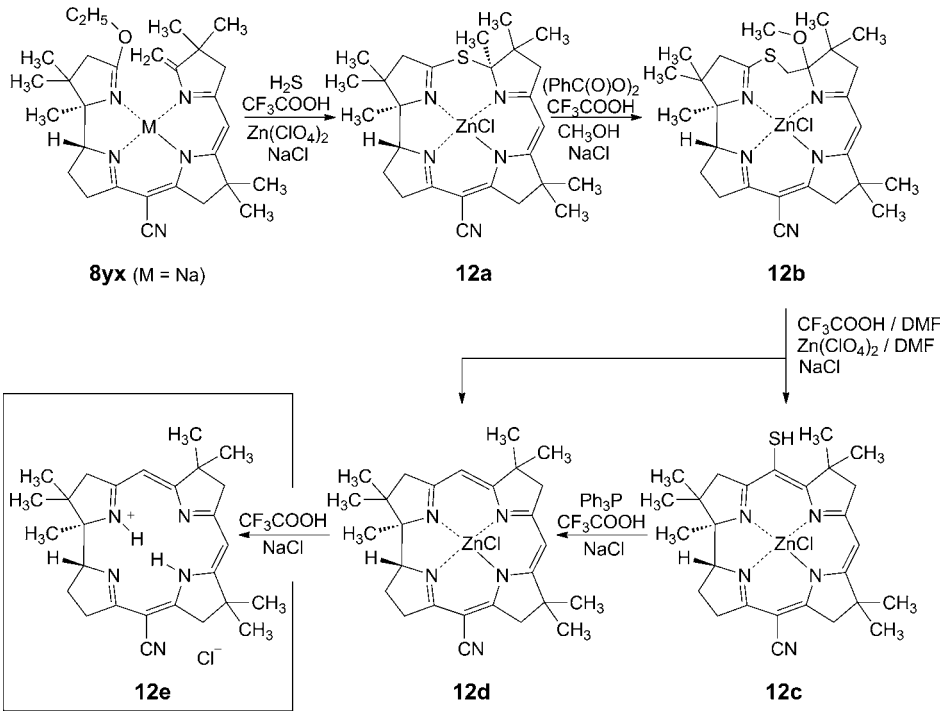


Fig. 12. All the corrin syntheses discussed thus far are syntheses of *complexes* of corrin ligands whereby the final $A \rightarrow B$ ring closure cannot dispense with the assistance of the strong template effect of a coordinating transition-metal ion. Corrin complexes of such transition metals are robust to a degree that the metal ion cannot be removed anymore without destruction of the ligand, this in sharp contrast to the corresponding *A*/*B*-secocorrin complexes. The problem of a synthesis of corrins could not really be considered to be solved, as long as a synthesis of the metal-free corrin ligand would be out of reach. In 1965, *Toohey* [151], working in the laboratory of *Barker* in the wake of the discovery of the coenzyme form of vitamin B_{12}, isolated Co-free natural corrins from photosynthesizing bacteria, an advent that added to the challenge of developing a synthesis of metal-free corrins. To achieve this, a new method for the $A \rightarrow B$ ring closure would have to be found, one that would work within an *A*/*B*-secocorrin complex of a non-transition-metal ion such as Zn^{II} to form a corresponding corrin complex from which the coordinating metal might be removable under mild conditions. Such a method became available by the 'intramolecularization' of the *A*/*B*-secocorrin → corrin imido-ester/enamine condensation through the 'sulfide contraction' pathway, the general method of thiolactam/enamide coupling developed in 1966 as the solution for the synthesis of the *B*/*C* component for the Harvard/ETH B_{12} project (see *Fig. 16–18* below).

Working for the heptamethyl series, *Albert Fischli* [9][88], by adapting the sulfide-contraction method to the $A \rightarrow B$ ring closure, succeeded in 1967 to synthesize the Zn^{II}-corrin complex **12e** which, under mild acidic conditions, could be demetalated to

the metal-free corrinium cation **12e**. An X-ray structure analysis of the hydrobromide of **12e** in *Hodgkin*'s laboratory in Oxford corroborated the constitutional assignment and revealed unforeseen conformational details of the metal-free corrin ligand [221][17]. The procedure for the reaction sequence **8yx** → **12a** → (**12b**) → **12c** → **12d** → **12e**, as optimized by *Hansueli Blaser* in his thesis work [95], appears quite complex, considering its sequential demand for reagents and conditions, yet turned out to be remarkably reliable and efficient. In fact, the *A* → *B* ring closure *via* sulfide contraction, as explored by *Peter Schneider* [97][17] in the natural series (*cf. Chapt. 3*), became the method of choice for closing the corrin ring in the *A*/*D* + *B*/*C* variant of the B_{12} synthesis [208c].

Reaction conditions [9][88][95]: **8yx** (M = Na) → **12a**: a) CF_3COOH, DMF; b) H_2S, 50°, closed tube; c) EtONa, EtOH, r.t.; d) $Zn(ClO_4)_2 \cdot (CH_3CN)_6$, EtOH, → NaCl, H_2O; 54% [88]; **12a** → **12b**: Bz_2O_2, CF_3COOH, CH_2Cl_2, r.t.; → MeOH, → NaCl, H_2O; 72% [95]; **12b** → **12c**: CF_3COOH, DMF, 80°, → $Zn(ClO_4)_2$, DMF, → CH_2Cl_2, NaCl, H_2O; 52% **12c**, besides 10% of **12d** [95]; **12c** → **12d**: Ph_3P, 0.1 equiv. CF_3COOH, $CHCl_3$, reflux, → NaCl, H_2O; 86% [88]; **12d** → **12e**: CF_3COOH, MeCN, r.t., → NaCl, H_2O; 92% [88].

Dinor-*A*/*B*-secocobyrinsäure-heptamethyl-ester präparativ optimiert worden [17]. Als Ergebnis war am Schluss ein Verfahren zur Hand, das in seiner experimenteIlen Ausführung zwar alles andere als einfach war, das dafür aber so zuverlässig und so ergiebig arbeitete, dass es in der Schlussphase des Vitamin B_{12}-Projekts an der Harvard zum (*A* → *B*)-Ringschlussverfahren der Wahl avancierte [208c].

Mit dem präparativen Zugang zu metallfreien Corrinium-Salzen des Konstitutionstyps **12e** war der Weg frei für Untersuchungen über die Einführung von Metall-Ionen in das Corrin-Ligandsystem und damit zu einer reichhaltigen Palette von neuen Corrin-Komplexen **13a**. *Fig. 13* orientiert über die damals hergestellten und z. T. in der Corrin-Reihe erstmals spektroskopisch charakterisierten Metall-Komplexe [95] und gibt zugleich auch Auskunft über die präparativ wichtige Frage, welche der eingeführten Metall-Ionen aus dem Corrin-Ligandsystem ohne dessen Zerstörung wieder entfernt werden können (vgl. *Teil V* dieser Reihe).

2.4. C-*Methylierung von* meso-*Stellungen des Chromophor-Systems von Dicyano-*Co^{III}*-1,2,2,7,7,12,12-heptamethylcorrinat*.

Wie schon erwähnt, hatte sich ab 1966 unter den bis dahin ausgearbeiteten Corrin-Synthesen mit drei unterschiedlichen Varianten von *A*/*D*-Komponenten aus präparativen Gründen die Heptamethyl-Version durchgesetzt. In ihr war zudem die Anzahl und Verteilung der Me-Substituenten an der Ligandperipherie dem Substitutionsmuster der natürlichen Corrinoide am ähnlichsten, womit sich das Dicyano-Co^{III}-corrinat dieser Reihe am ehesten für Modellstudien zur regioselektiven Einführung von Me-Gruppen in den Corrin-Chromophor eignete, und zwar Methylierung an jenen Stellen, an welchen auch die Vitamin B_{12}-Molekel seine beiden chromophorgebundenen Me-Gruppen aufweist. Solche Modellstudien hat *Ernst-Ludwig Winnacker* [90] am Heptamethylcorrinat **9d** durchgeführt und dabei gezeigt, wie man auf dem Wege einer Ag^+-assistierten Alkylierung des Co^{III}-corrinats mit Chloromethyl-phenyl-sulfid und anschliessender reduktiver Desulfurierung (*Raney*-Ni und H_2) je eine Me-Gruppe in

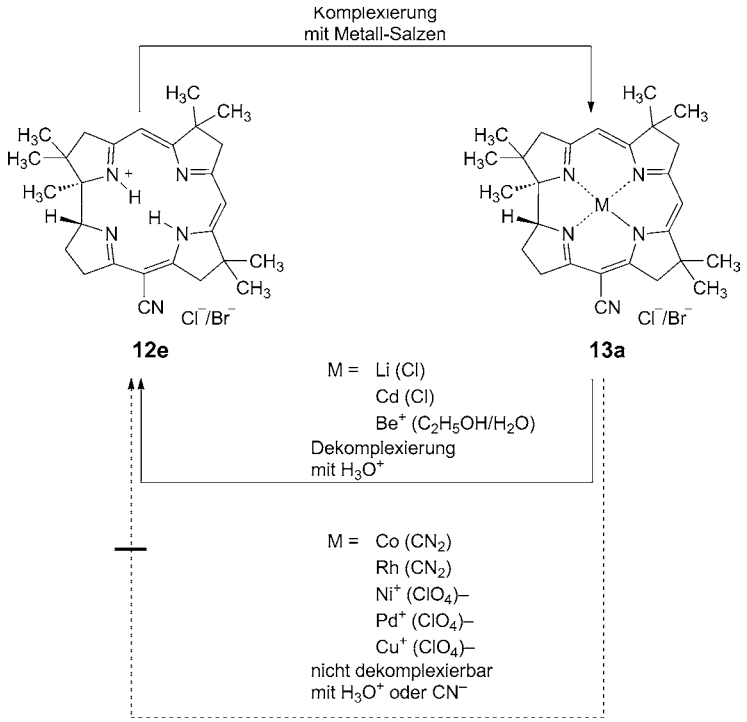


Fig. 13. Once a metal-free corrin had become available by synthesis, the introduction of various metal ions in the ligand to form different corrin complexes was studied, as well as the question of which of the metal ions could – and which could not – be removed again from the respective complex without destroying the ligand. Metal ions such a Li^{I}, Zn^{II}, Cd^{II}, and Be^{II} were easily removed under acidolytic/solvolytic conditions, transition metal ions such as Co^{III}, Rh^{III}, Cu^{II}, Ni^{II}, and Pd^{II} were not. Much later, in the course of the post-B_{12} work on corrins, it was observed that the dicyano-Co^{III}-corrin complex **9d** could in fact be (reductively) decomplexed in good yield to the hydrochloride of the corresponding heptamethylcorrinium cation by treatment with propane-1,3-dithiol/HCl, whereas under similar conditions the corresponding Ni^{II} complex remained unchanged [53].

Reaction conditions [95][106]: **12e** → **13a**: M = Li: LiOH (solid), $CHCl_3$, N_2, r.t.; 81%; M = ZnCl: $Zn(ClO_4)_2 \cdot (CH_3CN)_4$, $EtN(^iPr)_2$, CH_3CN, r.t., NaCl, H_2O; 91%; M = CdCl: $Cd(ClO_4)_2 \cdot (H_2O)_3$, MeOH, Ar, r.t., NaCl, H_2O; 90% [106]; M = Be-(EtOH): $BeCl_3 \cdot (Et_2O)_2$, N_2, CH_3CN, $EtN(^iPr)_2$, EtOH/$NaClO_4$; 90% [106]; M = Ni^+: $Ni(CH_3COO)_2$, CH_3CN, 70°, $NaClO_4$, H_2O; 94%; M = Pd^+: $Pd(CH_3COO)_2$, EtOH, 70°, $NaClO_4$, H_2O; 94%; M = Cu^+: $Cu(ClO_4)_2 \cdot (H_2O)_6$, MeOH, r.t., $NaClO_4$, H_2O; 98%; M = $Co(CN)_2$: $Co(ClO_4)_2 \cdot (DMF)_6$, CH_3CN, Ar, r.t., NaCl, H_2O, air, KCN, H_2O; 83%; M = $Rh(CN)_2$: $RhCl(CO)_2$, Me_3COONa/Me_3COOH, 100°, KCN, MeOH, H_2O; 75%.

die *meso*-Stellungen C(5) und C(15) einführen kann (*Fig. 14*). Entscheidend für die Wahl des maskierten Methylierungsreagens war – vor allem im Hinblick auf die Anwendung einer solchen Methodik auf die Synthese des Vitamins B_{12} – die Forderung nach eindeutiger (chromatographischer) Auftrennbarkeit der Produktgemische, in welchen mono- und mehrfach methylierte, sowie auch nicht-methylierte Komponenten zu erwarten sein würden; denn eine Trennung solcher Gemische würde bei direkter Einführung von Me-Gruppen schwierig sein, insbesondere bei entsprechenden Methylierungsgemischen in der natürlichen Reihe. Bei der (Phenylsulfanyl)methylierung des Modellsubstrats **9d** war in der Tat die chromatographische Isolierung des Monosubstitutionsprodukts **14a** vor dessen reduktiver Umwandlung in das Me-Derivat **14b** sehr einfach.

Die *meso*-Stellung C(15) zwischen den Ringen *C* und *D* in **9d** ist sterisch weniger gehindert als C(5) zwischen den Ringen *A* und *B*; dementsprechend reagiert erstere mit dem elektrophilen Agens rascher als letztere. Das 5,15-Dimethylierungsprodukt **14c** wurde durch Wiederholung der zweistufigen Reaktionsfolge ausgehend von **14b** erhalten. Dieses Prinzip der zweistufigen Methylierung der beiden *meso*-Stellungen des Corrin-Chromophors hat sich später – wenn auch in modifizierter Form – im 'Ernstfall' des B_{12}-Projekts bewährt.

Wir haben in der Modellreihe eine weitere Variante der Methylierung der *meso*-Stellungen des Dicyano-Co^{III}-corrinats **9d** überprüft, und zwar unter Verwendung eines kurz zuvor im Zusammenhang mit einer anderen Problemstellung entdeckten Reagens, dem in kristalliner Form erhältlichen (Dimethyl)(methyliden)iminium-iodid [18] (*Fig. 14*). Das Reagens reagierte mit **9d** regioselektiv zu **14d**, und die reduktive Entfernung von dessen Me_2N-Gruppe (katalytische Hydrierung mit Pd) ergab wiederum **14b**. Eine Methylierung der *meso*-Stellung zwischen den Ringen *A* und *B* auf diesem Wege war überraschenderweise nicht zu erreichen. Die Ursache dürfte in einer höheren Empfindlichkeit der Reaktion auf sterische Hinderung liegen.

Für die Konstitutionszuordnung der Methylierungsprodukte war die Verfügbarkeit des in einem anderen Zusammenhang *de novo* synthetisierten, authentischen 5-Methylcorrinats **14e** hilfreich; seine Herstellung aus den Komponenten **8n** ($R = Me$, $R^1 = H$) und der *C*-methylierten *B*/*C*-Komponente **14f** stammt aus Versuchen (vgl. *Fig. 8* in *Teil IV*), die im Zusammenhang mit der Frage durchgeführt worden waren, ob das Konzept der Corrin-Synthese *via* ($A \rightarrow B$)-Ringschluss auch mit einer *B*/*C*-Komponente mit Ethyliden- statt Methyliden-Gruppe realisierbar sein würde. Die dabei erzielte geringe Ausbeute des ($A \rightarrow B$)-Ringschlusses bestärkte die Richtigkeit der ursprünglichen B_{12}-Synthese-Planung, wonach die beiden *meso*-Me-Gruppen am Corrin-Chromophor des Vitamins in der Endphase der Synthese einzuführen sein würden.

Anhand von Co^{III}- und Ni^{II}-Komplexen **15a** – **15c** wurden einige zentrale chemische Eigenschaften des Corrin-Ligandsystems charakterisiert (*Fig. 15*). So ermittelte man in ^{1}H-NMR-spektroskopisch verfolgten Deuterierungsexperimenten in saurem Medium die relative (offenbar zur Hauptsache sterisch kontrollierte) nukleophile Reaktionsbereitschaft der drei *meso*-Stellungen im Sinne der Reihenfolge $C(15) > C(5) \approx C(10)$. Deuterierungsexperimente in basischem Medium belegten die selektive Deprotonierbarkeit an C(8) im Ring *B*. Wichtig für die konstitutionelle Interpretation der Deuterierungen war die Möglichkeit der regioselektiven Einführung der CN-Gruppe

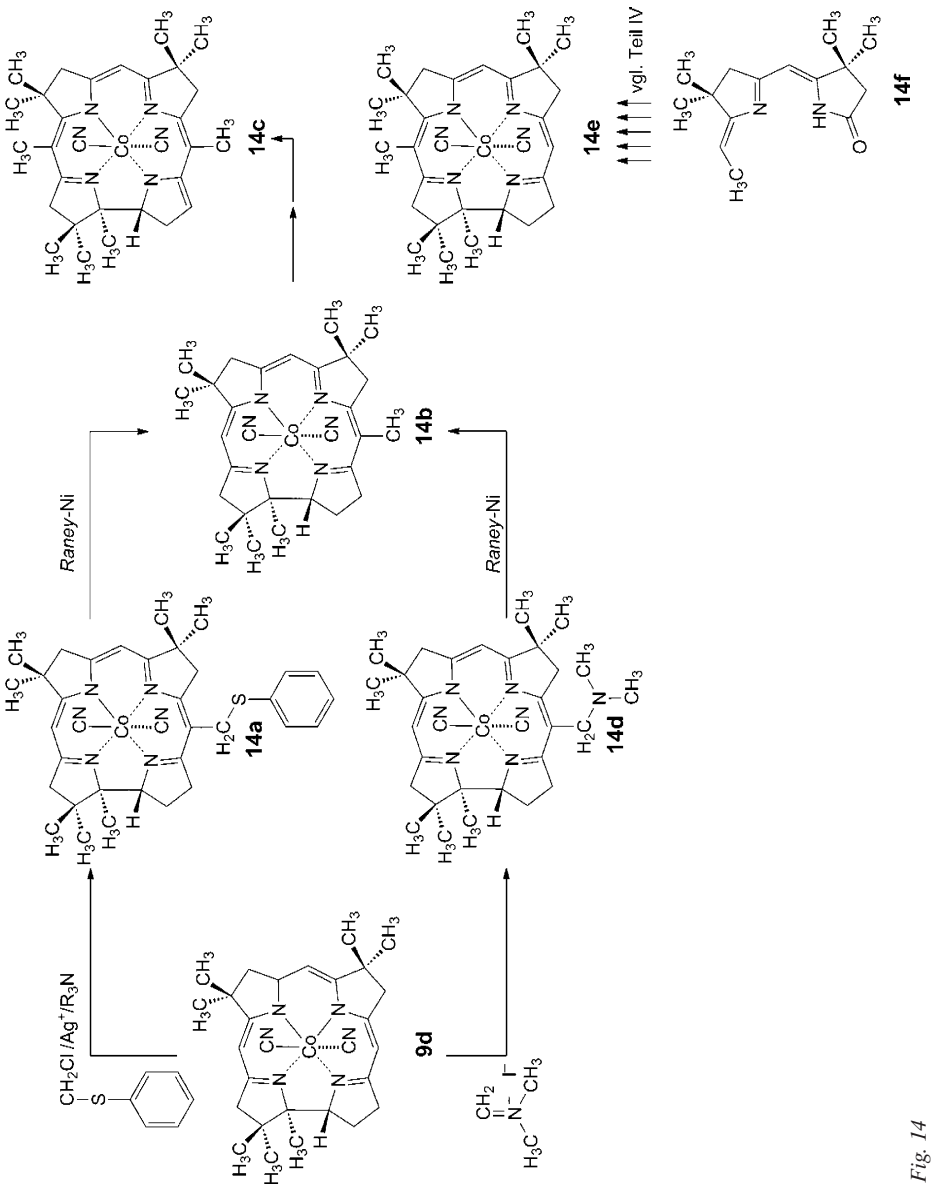

14c
14e
vgl. Teil IV
14f
Raney-Ni
14b
Raney-Ni
14a
14d
9d
CH2Cl /Ag+ /R3N

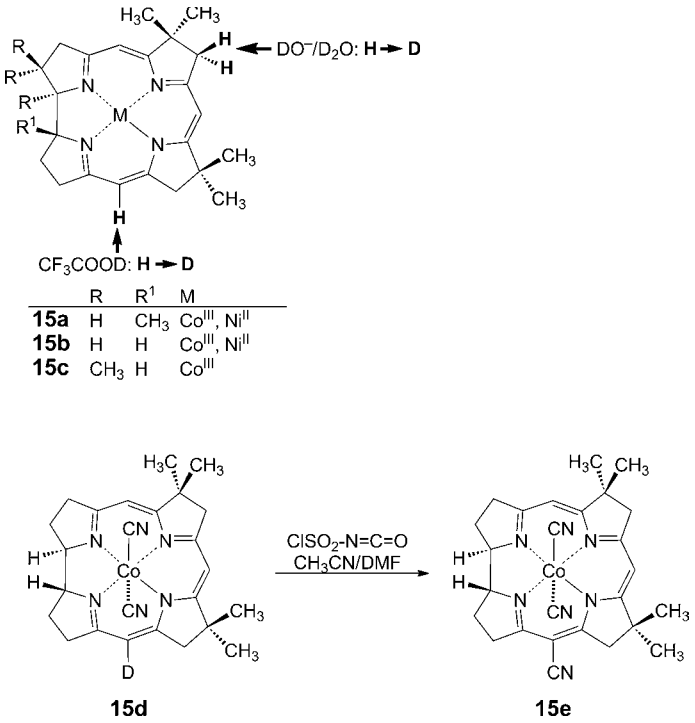
Fig. 14

Fig. 14. Not only was the pathway to dicyano-Co^{III}-corrin complexes in the heptamethyl series the most efficient of the three corrin syntheses discussed thus far, the dicyano-Co^{III} complex **9d** of this series with its seven peripheral Me groups and the three free *meso*-positions was also the most suitable model substrate for exploring methods for the introduction of Me groups at C(5) an C(15) of the corrin chromophor. This problem could be foreseen to become crucial in the end phase of the cobyric acid synthesis. Since especially in the natural series a separation of mixtures consisting of non-, mono-, and dimethylated derivatives would be foreseeably difficult, methylation methods were needed that would proceed *via* intermediates that would be easily purified by chromatography. Such a procedure was developed by *Ernst-Ludwig Winnacker* in his thesis work [90]: electrophilic substitution by chloromethyl phenyl sulfide in the presence of $Ag^+BF_4^-$, followed by hydrogenolysis with *Raney*-Ni, generated the methyl derivative **14b** from **9d** *via* the isolated and purified intermediate **14a** in an acceptable overall yield [90][17], selecting the sterically least hindered *meso*-position C(15) between rings *C* and *D* as the preferred reaction site. Applying the procedure to the 15-monomethyl derivative **14b** under slightly more severe conditions resulted in substitution at C(5) as well as C(10) in a ratio of *ca.* 5 : 1. The 5,15-dimethyl derivative **14c** could be secured in pure form (though in low yield) by separating the intermediates before hydrogenolysis. Side-products of mechanistically exotic origin (see Fig. 13 in *Part V*) pointed to a complex overall process. These observations made in the model series provided the starting point for attacking the methylation problem in the natural series. There, the problem's solution was found in the replacement of the reagent chloromethyl phenyl sulfide by chloromethyl phenyl ether [103] (see *Chapt. 3*, below).

When in a completely different context the crystalline *Mannich* salt (dimethyl)(methylidene)iminium iodide became available in our laboratory [18], it was tested as an alternative reagent for a two-step introduction of Me groups in the corrin chromophore. It reacted smoothly with **9d** giving regioselectively and in high yield **14d**, which, after hydrogenolytic removal of Me_2NH, afforded again **14b**. Disappointingly, the reagent could not be brought to react again with **14b**. This failure was pointing to a high sensitivity of electrophilic substitutions by this reagent to steric hindrance, in the present system exerted by the geminal dimethyl group near C(5) and C(10).

Constitutional assignment to methyl derivatives by ^{1}H-NMR spectroscopy was crucial in this methylation study and, in fact, greatly assisted by the availability of the complex **14e** in which the position of the chromophore-bound Me group was unambiguously known, since this corrin derivative had been obtained by an *ab-initio* synthesis, using **14f** (*cf.* Fig. 8 in *Part IV* of this series) as the *B*/*C* component.

Reaction conditions [90]: **9d** → **14a**: chloromethyl phenyl sulfide, $Ag^+BF_4^-$, $EtN(^iPr)_2$, Me_3CN, N_2, r.t.; 50%, besides 2–3% 5,15-bis(phenylsulfanyl)methyl derivative; **14a** → **14b**: *Raney*-Ni, EtOH, 0°, → KCN, EtOH, air, −15°; 84%; **14b** → **14c**: a) chloromethyl phenyl sulfide, $Ag^+BF_4^-$, $EtN(^iPr)_2$, CH_3CN, 40°, 30% mixture of 15-methyl-5- and -10-[(phenylsulfanyl)methyl] derivative, besides *ca.* 60% starting material; b) 15-methyl-5-[(phenylsulfanyl)methyl] derivative + *Raney*-Ni, EtOH, 0° → KCN, EtOH, air, −15°; 85%; **9d** → **14d**: (dimethyl)(methylidene)iminium iodide, CH_2Cl_2, N_2, r.t. → KCN, H_2O; 85% [18]; **14d** → **14b**: Pd-C, MeOH, Ar, H_2 (1 Torr), r.t., → KCN, MeOH, H_2O; 47% [18].



	R	R^1	M
15a	H	CH_3	Co^{III}, Ni^{II}
15b	H	H	Co^{III}, Ni^{II}
15c	CH_3	H	Co^{III}

Fig. 15. The sensitivity of the corrin ligand in dicyano-Co^{III}- and -Ni^{II}-complexes towards deprotonation/deuteration under basic condition and towards deuteration/protonation in the presence of acid were studied, as soon as complexes **15a** (R = H, R^1 = Me) and **15b** (R = H, R^1 = H) had become available in the penta- and tetramethyl series, respectively. Such experiments were taken up again later in the heptamethyl series with the dicyano-Co^{III}-corrinate **15c** (R = Me_3, R^1 = H). Reference point for the ^{1}H-NMR-spectroscopic assignments in complexes **15a**–**15c** was the unique and characteristic broadening of the signal of the vinyl H-atom at C(15), due to allylic coupling with the adjacent methylene at C(13) in ring *C* through the C(14),C(15) bond which has a higher π-bond order than the C(9),C(10) bond [218]. Chemical assistance for the assignments came from transformations such as **15d** → **15e**. Exposition of complexes **15a**–**15d** to chlorosulfonyl isocyanate in the presence of DMF [222] smoothly and regioselectively introduced a CN group betweeen rings *C* and *D*, which is the position that unambigously bears a CN substituent in *ab-initio* synthesized corrin complexes. As in the *C*-methylation studies mentioned above, the *meso*-position C(15) in dicyano-Co^{III}-corrinate **15b** reacted in deuteration experiments under acidic conditions fastest among the three *meso*-positions, and C(5) in the dicyano-Co^{III}-15-methylcorrinate **14b** of the heptamethyl series reacted about twice as fast as the *meso*-position C(10). For both the Co^{III}-corrinate **15a** of the tetramethyl series and the Ni^{II}-corrinate **15b** of the pentamethyl series, CH_2(8) was shown to be the preferred site of deuteration in basic media (*cf.* Figs. 9, 10, and 15 in *Part V* of this series).

Reaction condition: **15d** → **15e**: Chlorosulfonyl isocyanate, MeCN, r.t., → DMF, r.t., → KCN, H_2O; 86%.

an C(15) der Substratkomplexe mit Hilfe des *Lohhaus*'schen Reagens Chlorosulfonylisocyanat [222] (vgl. **15d** → **15e**); dies ermöglichte eine konstitutionelle Verknüpfung der Substratkomplexe mit den entsprechenden durch *ab initio* synthetisierten Komplexen eindeutiger Konstitution. Im Zusammenhang mit diesen experimentellen Arbeiten hatte damals *Reinhart Keese* [223] eine HMO-Studie veröffentlicht, deren Ergebnisse mit den experimentell beobachteten Selektivitäten bei der Deuterierung des Corrin-Chromophors und der Deprotonierung von dessen allylischen Positionen in bemerkenswertem Ausmass übereinstimmten.

2.5. *Corrin-Synthese* via *(*A → D*)-Ringschluss: Corrin-Chromophor-Aufbau nach der (*B/C + A + D → ABCD*)-Strategie mit der 'Sulfid-Kontraktion'-Methode.*

Wie eingangs bereits angedeutet, bietet die Geschichte der Entwicklung der 'Sulfid-Kontraktion'-Methode zur Konstruktion des Chromophorsystems des Vitamins B_{12} ein Beispiel dafür, wie bei der Synthese einer komplexen Naturstoff-Struktur die vorgängige Erprobung eines Syntheseweges an einer strukturell vereinfachten Modellzielstruktur entscheidende Inhalte des Entdeckungspotentials synthetischer Naturstoff-Forschung verpassen kann. Zwar haben die Untersuchungen über die Eignung der Imidoester–Enamin-Kondensation (*Fig. 5*) für den Aufbau des Corrin-Chromophors vor allem auch die Anwendungsgrenzen der Kondensationsmethode aufgezeigt (*Fig. 6*), dennoch haben die ersten Synthesen von Corrin-Komplexen (*Fig. 8* und *9*) das Potential dieses Reaktionstyps für den Aufbau des Corrin-Chromophors überzeugend nachgewiesen. Als ebenfalls ausserhalb dieser Anwendungsgrenzen liegend hatte sich vor allem auch die Herstellung der all diesen Synthesen gemeinsamen *B*/*C*-Komponente erwiesen; doch war es relativ leicht möglich, diese Hürde auf methodisch konventionellem Wege zu umgehen (*Fig. 8*). Zwar wurde kurz darauf das Ziel der Verknüpfung der Ringe *B* und *C* der ursprünglichen Planung gemäss in einem leicht modifizierten Ring-*B*-Modell mittels der Imidoester–Enamin-Kondensation wenigstens grundsätzlich erreicht (*Fig. 6*), zum praktischen Einsatz in einer Corrin-Synthese war jene modifizierte *B*/*C*-Komponente allerdings nicht mehr gelangt. Grund hierfür war vor allem die 1966 erfolgte Entwicklung der Sulfid-Kontraktion-Methode im Rahmen des Vitamin B_{12}-Projekts, wodurch für das Problem einer effizienten präparativen Herstellung der *B*/*C*-Komponente sowohl für die Modellreihe, als auch für die B_{12}-Synthese selbst, eine Lösung gefunden wurde, die einem Optimum nahe kommt (*Fig. 16*).

Die für die Verknüpfung der Vorläufer **16a** und **16b** der Ringe *B* und *C* im Vitamin B_{12}-Projekt vorgegebenen konstitutionellenVoraussetzungen entsprachen zwar durchaus der ursprünglichen Planung für die Synthese der Modell-Corrine, diese Voraussetzungen waren aber doch auch durch die Gegebenheiten ihrer synthetischen Herkunft bestimmt[29]). So war in vielfältig variierten, exploratorischen Versuchen

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[29]) Über den Stand der ETH-Arbeiten am B_{12}-Projekt im Sommer 1967 und den Stand der Zusammenarbeit mit der Harvard-Gruppe im Herbst 1968, vgl. [11], im Herbst 1969, vgl. [17]. Über die beiden für den Ring-*B*-Vorläufer **16a** an der ETH entwickelten Synthesen, vgl. die Dissertationen von *P. Löliger* [87] (Synthese des Enantiomers mit korrektem Chiralitätssinn) sowie von *A. Wick* [82] (Alternative Synthese des Racemats *via* Amidacetal-*Claisen*-Umlagerung), und über die Überführung des Ring-*B*-Vorläufers **16a** in den Ring-C-Vorläufer **16b** und dessen

versucht worden, die aus **16a** bzw. dem entsprechenden Thiolactam **16e** leicht zugänglichen Imidoester- und Imidothioester-Derivate **16d** des Ring-*B*-Vorläufers mit dem in 'beliebigen Mengen' zur Verfügung stehenden und deshalb als Ring-*C*-Vorläufermodell benutzten Methyliden-lactam **6e** zu verknüpfen: ohne jeglichen Erfolg. Da gerade zu jener Zeit (erste Hälfte des Jahres 1965), in der Modellreihe endlich die Synthese einer *B*/*C*-Komponente nach dem ursprünglich vorgesehenen Prinzip der Imidoester–Enamin-Kondensation gelungen war (vgl. die Reaktionsfolge **6e** → **6k** in *Fig. 6*), schien im B_{12}-Projekt auf Grund dieses Ergebnisses als nächste Möglichkeit die Umwandlung eines Imido- oder Imidothioesters **16d** (X = O oder S) in ein entsprechendes C_β-Cyano-enamin-Derivat (Strukturtyp **6i** in *Fig. 6*) und dessen Kondensation mit einem entsprechenden Ring-*C*-Vorläufermodell (**6a** in *Fig. 6*) anzustehen. Doch schon der erste Schritt in dieser Richtung, nämlich die Kondensation von Imidoester-Derivaten **16d** mit dem *tert*-Butyl-ester der 2-Cyanoessigsäure erfolgte selbst bei erhöhter Temperatur kaum, dies in deutlichem Gegensatz zur Modellreihe, offenbar als Folge höherer sterischer Behinderung. Zu einer weiteren Bearbeitung in dieser Richtung kam es nicht, denn inzwischen war auf konzeptueller Ebene mit der Idee einer '*Intramolekularisierung*' der Imidoester–Enamin-Kondensation die Möglichkeit einer Lösung des Problems aufgetaucht [11]: durch oxidative Aktivierung des Thioamid-S-Atoms sollte versucht werden, die Imidothioester-Komponente vorerst durch eine (S → C)-Kopplung mittels Reaktionen des Typs **16e** → **16f** und **16f** + **6e** (als Modell) → **16g** mit der Enamid-Komponente zu verknüpfen, um anschliessend in einer nunmehr *intramolekular* ablaufenden Imidothioester–Enamid-C,C-Kondensation die Knüpfung der kritischen (C–C)-Bindung zu erreichen. Primärprodukt eines solchen Prozesses würde ein kurzlebiges Episulfid **16h** sein, das entweder in ein Sulfanyl-vinamidin-Derivat sich umlagern, oder sein S-Atom auf ein externes Thiophil unter Ausbildung des Zielprodukts **16i** übertragen könnte. Diese Strategie entsprang dem Wissen um das Phänomen, wonach C,C-Bindungen zwischen Reaktionszentren organischer Moleküle sich generell leichter bilden, wenn die entsprechenden Reaktionsprozesse *intra*molekular statt *inter*molekular ablaufen können. Relevante Informationen aus der Literatur zur Frage des primären Kopplungsschritts betrafen die Addition von Sulfenyl-halogeniden an olefinische (C=C)-Bindungen [224]. Es sind diese Reaktionen, die offenbar elektrophil ausgelöste Additionen sind und im Spezialfall der gegenüber starken Elektrophilen empfindlichen Methyliden-lactam (C=C)-Bindung des Ring-*C*-Vorläufers **16b** (bzw. seinem Modell **6e**) wohl als Substitutionen und nicht als Additionen ablaufen würden[30]).

Eingehende exploratorische Versuche (in der *ent*-Reihe) durch *Peter Löliger*[31]) [87] zu einer solchen oxidativ induzierten Kopplung des Thiolactams *ent*-**16e** mit dem

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Chiralitätsbestimmung, vgl. die Dissertation von *P. Dubs* [92]. Das an der ETH für die *präparative* Herstellung der *B*/C-Komponente **16c** eingesetzte Material des Ring-*C*-Vorläufers wurde an der Harvard ausgehend von (+)-Campherchinon nach einem Verfahren hergestellt [208a], das eine Modifikation der in der von *Cornforth* und *Pelter* [178] [179] um 1960 entwickelten Synthese des gleichen Ring-*C*-Vorläufers war.

[30]) Vgl. die durch Protonen katalysierte Dimerisation des Methyliden-lactams **6e** zu **10a** (*Fig. 10*).

[31]) *Peter Löliger*, Doktorat, 22.6.1964 – 25.10.1967 [87].

Methyliden-lactam **6e** zu *ent*-**16g** *via* Sulfenyl-Derivate des Typs *ent*-**16f** umfassten die direkte Halogenierung des S-Atoms, oder dessen Überführung in ein entsprechendes Oxid, gefolgt von *O*-Acetylierung. Als hoch labile Zwischenprodukte wurden diese Sulfenyl-Derivate nicht isoliert, sondern direkt mit **6e** (als Modell für Ring *C*) umgesetzt. Zwar waren solche Kopplungsversuche nicht durchgehend erfolglos (so konnte *ent*-**16g** erstmals aus der Umsetzung des Sulfenyl-bromids *ent*-**16f** (Y = Br) mit **6e** in *ca.* 10% Ausbeute isoliert und charakterisiert werden [87]), doch der eigentliche Durchbruch (erste Hälfte 1966) erfolgte mit *Bernard Golding*s[32]) Fund einer Literaturangabe über die Oxydation von *N*,*N*′-Diphenylthioharnstoff mit Dibenzoylperoxid (Bz_2O_2) zum entsprechenden Disulfid [225] und der Anwendung dieses Oxidationsmittels auf unser Problem. Nahezu quantitativ bildete sich aus dem Thiolactam *ent*-**16e** das entsprechende Disulfid, und dieses ergab – zusammen mit dem Ring-*C*-Modell **6e** – in hoher Ausbeute das gesuchte S-überbrückte Kopplungsprodukt *ent*-**16g**. Beim Erhitzen mit $(MeO)_3P$ in Xylol ging letzteres unter S-Transfer und Bildung einer (C,C)-Bindung – sozusagen einer 'Kontraktion' der Iminyl-vinylsulfid-Kette zum Vinamidin-Chromophor – in das Zielprodukt *ent*-**16i** über.

Einen durch die Summe späterer Erfahrungen (s.u.) erreichten Überblick auf das Reaktionsprinzip der *intramolekularisierten* Iminothioester–Enamin-Kondensation ('Sulfid-Kontraktion'-Methode) ist in *Fig. 17* dem Reaktionsprinzip der *intermolekularen* Imidoester–Enamin-Kondensation gegenübergestellt. Das zentrale Zwischenprodukt der intramolekularen Version ist ein Carbiminoyl-enaminyl-sulfid, das auf zwei verschiedenen und konstitutionell zueinander komplementären Wegen zugänglich ist: entweder durch oxidative oder durch alkylative Kopplung der Kondensationspartner. Erstere erfordert die oxidative Aktivierung des Thioamid-Partners, letztere die (letztlich ebenfalls oxidative) Einführung einer elektrophilen Abgangsgruppe am C(β)-Atom des Enamin- bezw. Enamid-Partners. Ob das obligate (nicht zu beobachtende) Zwischenprodukt der Kontraktionsstufe, das Episulfid, sein S-Atom auf ein Thiophil überträgt oder sich zum Sulfanyl-vinamidin umlagert, hängt von der Konstitution des Substrats, den Reaktionsbedingungen und insbesondere von der Präsenz und der Natur des Thiophils ab. Für die generelle Verwendbarkeit der Methode der Sulfid-Kontraktion zum Aufbau des Corrin-Chromophors ist wichtig, dass die *intramolekularisierte* Reaktion im entscheidenden Unterschied zur *intermolekularen* Imidoester–Enamin-Kondensation sowohl mit *N*-Alkyl- wie auch *N*-Acylenamin-Partnern erfolgreich sein kann. Die Methode erwies sich im Vitamin B_{12}-Projekt als Panacea des Corrin-Chromophoraufbaus: nicht nur die Verbrückung der Ringe *B* und *C* zur *B*/*C*-Komponente **16c**, sondern auch die Vinamidin-Brücken zwischen den Ringen *C* und *D* sowie *A* und *B* der B_{12}-Struktur wurden schliesslich nach dieser Methode gebildet [17][19][24][29][208b,c]. Seither hat das Kondensationsprinzip in der Synthetik eine allgemeinere Verbreitung mit Substrat-Partnern gefunden [226], die nicht zu Vinamidinen, sondern auf analogen Reaktionswegen auch zu vinylogen Amiden und konjugiert-enolisierten β-Dicarbonyl-Systemen führen [16].

In unserem Laboratorium war die Methode der (C,C)-Verknüpfung durch 'Sulfid-Kontraktion' als 'Intramolekularisierung' der Reaktionspfads einer intermolekularen

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[32]) *Bernard Golding*, Postdoktorat ETH, 7.1.1966 – 31.8.1967; vgl. Dissertation von *P. Löliger* [87].

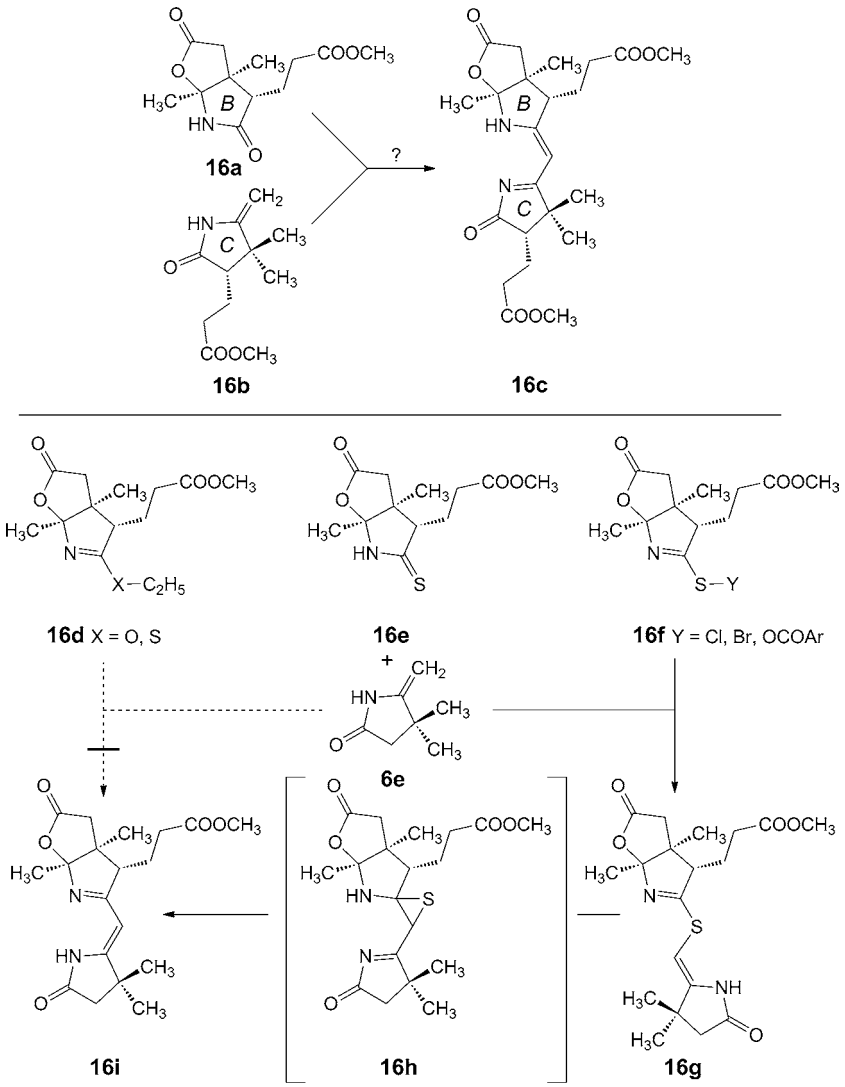

Fig. 16. The wall that the ETH group ran into, while attempting the coupling of the ring-*B* precursors with that of ring *C* for the synthesis of the *B*/*C* component in the natural series, was eventually overcome through an 'intramolecularization' of the imido-ester/enamine condensation concept by a method that we refer to as 'sulfide-contraction method'. Its origin is an instructive example of how model studies can miss the potential for discovery that research in natural products synthesis carries with it. The original planning, together with given circumstances in the natural series, had rendered structures **16a** and **16b** as the potential precursors of rings *B* and *C*, respectively. Extensive exploratory attempts (in the *ent*-series, in order to preserve the material of the natural series) were undertaken to couple imido-ester derivatives

ent-**16d** (X = O and S) with the achiral ene-lactam **6e** as (close) model of ring *C*, but to no avail. Neither had the direct coupling of type **16a** + **16b** → **16c** *via* an *intermolecular* imido-ester/enamide condensation been possible in the corrin model series. Part of the problem had been the propensity of the monocyclic ene-lactam **6e** to undergo a proton-catalyzed dimerization (*cf. Fig. 10*), for which reason acid catalysis for achieving the desired coupling was to be excluded. As discussed earlier (*cf. Fig. 6*), a solution to the problem eventually found in the model series was the reaction sequence **6e** → **6g** → **6h** → **6i** → **6k**. Adapting the problem in the natural series to that solution would have demanded imido-ester derivatives **16d** to first be condensed with *tert*-butyl 2-cyanoacetate, in analogy to the transformation **6g** → **6h** in the model series. Disappointingly, imido ester *ent*-**16d** underwent this otherwise smoothly proceeding condensation only very sluggishly, clearly as a consequence of the reaction's high sensitivity toward steric hindrance in the imido-ester partner.

It was in the context of this struggle that the concept of an *intramolecularization* of the method of an *intermolecular B* → *C* ring coupling *via* a imido thioester/enamide condensation was born. Assisting impulses came from the literature describing sulfenyl-halides to undergo electrophilic addition reactions to olefinic C=C bonds [224], as well as from our own earlier observations according to which the methylidene C-atom of **6e** is prone to react with strong electrophiles (*cf. Fig. 10*). It was assumed that converting thiolactam **16e** to a sulfinyl-halide derivatives of type **16f**, followed by *intermolecular* coupling at the S-atom with the methylidene C-atom of **6e** might produce **16g**, in which the stage would be set for an *intramolecular* imido thioester/enamide condensation. The (reversibly formed) product of such an *intramolecular* C,C-bond formation would be the episulfide **16h**, the S-atom of which might be retrieved by a thiophile present in the medium to form the targeted vinamidin structure **16i**.

In extensive attempts to realize this concept experimentally using (the *enantiomer* of) **16a** and the ene-lactam **6e** as the (close) model for ring *C*, the S → C coupling product *ent*-**16g** was isolated for the first time, albeit in low yield, in experiments carried out by *Peter Löliger* [[87], where thiolactam *ent*-**16e** was treated with bromine to form the sulfenyl bromide *ent*-**16f** (Y = Br) as the condensing electrophile. The preparative breakthrough, however, came early 1966 with the use of benzoyl peroxide (Bz_2O_2) as oxidant by *Bernhard Golding*[32]), who had spotted a report in the literature [225] concerning a thiourea to be cleanly oxidized by this reagent to the corresponding disulfide. Bz_2O_2 turned out to be the reagent of choice for achieving the coupling step *ent*-**16e** + **6e** → *ent*-**16g** in high yield and to discover that heating *ent*-**16g** in $(MeO)_3P$ leads to 'contraction' of this sulfide intermediate by transfer of the S-atom to the thiophile and thereby forming the (enantiomer of) vinamidin derivative **16i**, *i.e.*, *ent*-**16i**.

(C,C)-Verküpfung durch Imidoester–Enamin/oder Enamid-Kondensation konzipiert worden. Indessen erwies sich im Nachhinein wohl kaum eine methodische Entwicklung in der Syntheseforschung als mechanistisch so neuartig, dass diese keine Vorläufer hätte; so auch in diesem Fall. Eine Beobachtung relevanter Art findet sich bereits bei

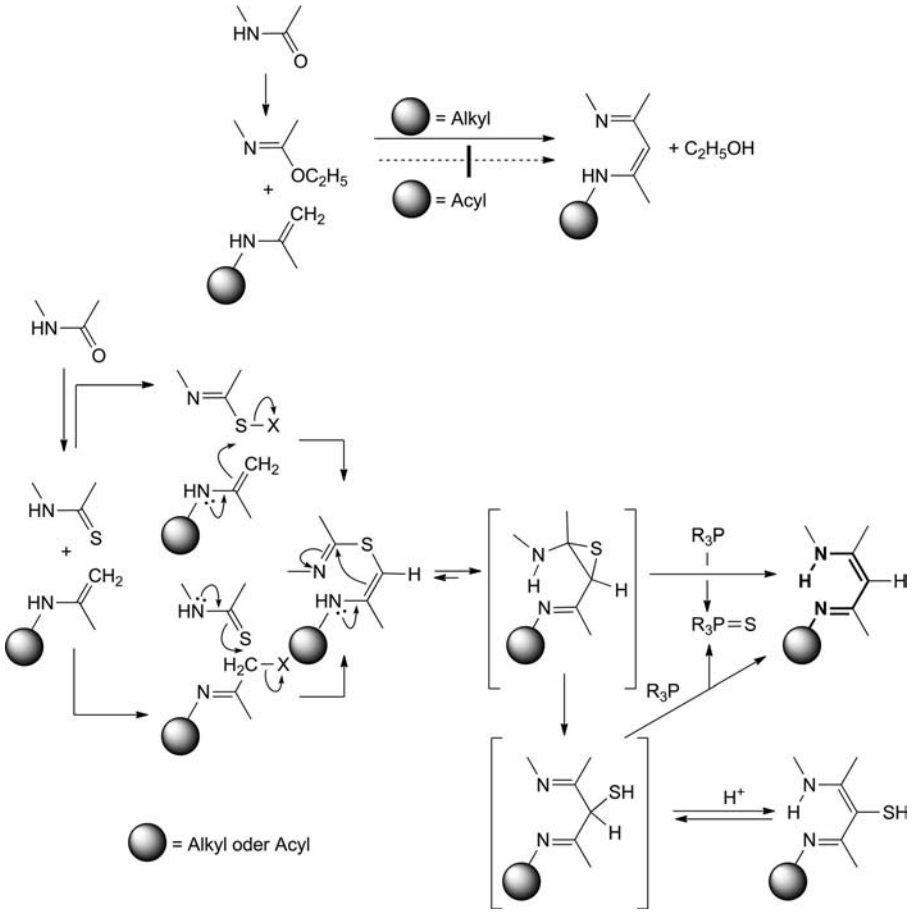

Fig. 17. This *Figure* juxtaposes in generalized form the two C,C-coupling reaction concepts for constructing the corrin chromophore system. This coupling process is either an *electrophilic* attack at the nucleophilic C-atom of the enamide or enamine partner by the oxidatively activated S-atom of the thioamide partner, or an *alkylative* attack at the S-atom of the thioamide partner by a *C*-halogenated enamide or enamine partner. In both variants, activation is provided by oxidative (or halogenative) activation of the one or the other partner, the coupling being brought about by an S_N2-type electrophilic attack either by C- on S-atom, or by S- on C-atom. The two variants are referred to as 'sulfide contraction *via oxidative* coupling' *vs.* 'sulfide contraction *via alkylative* coupling'. The ease by which the contraction step and the (potentially concomitant) transfer of the S-atom proceed strongly depends on constitutional circumstances and the nature of the thiophile. The latter may grasp the S-atom directly from the transient episulfide, or the latter may first rearrange to a 2-sulfanyl-1,3-diketimin that either delivers the S-atom to the thiophile or – in the absence of the latter – rearranges to a sulfanyl-vinamidin.

The 'sulfide contraction' method not only had a major impact on the progress of our work on the chemistry of synthetic corrins, it proved to be a *panacea* for the construction of the chromophore system in the syntheses of vitamin B_{12}, at the ETH [17][19][24][29], as well as at Harvard [208a,b,c]. Since then, the methodology has found wide applications also in other laboratories [226], especially after the extension of the scope of the method to potential 1,3-dicarbonyl systems had been published [16].

The 'sulfide contraction' method was conceived as an 'intramolecularization' of a C,C-bond formation *via* imido-ester/enamine (or enamide) condensation. As probably true for most developments in synthetic methodology, the 'novelties' involved will hardly ever turn out to be without precedents; this is certainly also true in the present case. The first relevant observation may be one made by *Staudinger* and *Siegwart* [227a] as early as 1920[33]). While many observations made in extended inverstigations on 'sulfur extrusion' reactions [227b] are closely related, a real precedent was observed in 1955 by *Knott* [227c] in his work on thiocyanin systems. Literature references on this and other work relevant in the present context are to be found in our 'sulfide contraction' publication of 1971 [16b].

Staudinger und *Siegwart* aus dem Jahr 1920 [227a][33]). Relevant sind auch zahlreiche Arbeiten, in denen die Bildung von (C,C)-Bindungen als Folge einer '*sulfur extrusion*' beschrieben wurden [227b]. Eigentliche Vorläufer-Befunde über die Reaktionsfolge der 'Sulfid-Kontraktion' sind indessen die von *Knott* [227c] im Zusammenhang mit der Herstellung von Thiocyanin-Systemen gemachten Beobachtungen aus dem Jahre 1955. In unserer ersten Publikation über die '*Sulfid-Kontraktion via alkylative Kupplung*' [16b] sind Literaturangaben über diese und andereVorläuferarbeiten zusammengestellt.

Die Entwicklung der Sulfid-Kontraktion-Methode hatte nicht nur eine effiziente Synthese der in beiden Varianten der B_{12}-Synthese verwendeten *B*/*C*-Komponente ermöglicht (vgl. *Fig. 16*), sondern auch die corrinsynthetischen Arbeiten in der Modellreihe beflügelt. Was die neue Methode allem voran ermöglichte, war der Aufbau eines tetracylischen *A*/*D*-secocorrinoiden Modellligand-Systems für das wohl riskanteste Unternehmen in unseren corrinsynthetischen Modelluntersuchungen überhaupt: der Erprobung der lichtinduzierten (*A*/*D*-Secocorrin → Corrin)-Cyclo-isomerisierung (s.u.). Vorab hat die Sulfid-Kontraktion-Methode der präparativen Herstellung der damals bereits bewährten Modell-*B*/*C*-Komponente **6f** einen Weg eröffnet, der viel effizienter als der früher begangene war, und in welchem das Methyliden-lactam **6e** nunmehr als gleichwertiger Vorläufer beider Ringe zum Zuge kommen konnte (vgl. die Reaktionsfolge **6e** → **18a** → **18b** → (**18c**) + **6e** → **18d** → **18e** → **6f** in *Fig. 18*). Als Vorläufer des Ringes *B* gelangte dabei **6e** in reaktionsgerecht durch eine CN-Gruppe geschützter Form als Thiolactam **18b**[34]) um Einsatz [14]. Oxidation dieses Thiolactams mit Bz_2O_2 in Gegenwart des Methyliden-lactams **6e** führte zum überbrückten Kopplungsprodukt **18d** in über 70% Ausbeute, die anschliessende Kontraktion zu **18e** und Freisetzung der Methyliden-Gruppe zu **6f** über beide Stufen

[33]) *Staudinger* und *Siegwart* [227a] beobachteten, dass Thiobenzophenon, bei Raumtemperatur mit Diphenyldiazomethan umgesetzt, zum Episulfid von Tetraphenylethylen, und dieses, auf 175° erhitzt, unter Verlust des Schwefels zu Tetraphenylethylen führt.

ebenfalls. Der Kopplung voraus geht die oxidative Umwandlung des Thiolactams **18b** in das die Methyliden-Gruppe von **6e** attackierende Disulfid **18c**, welches isoliert werden kann, aber nicht unbedingt muss [14][98]. Eine später ausgearbeitete, alternative Kopplungsvariante geht von dem durch Iodierung von **6e** leicht zugänglichen (Iodomethyliden)-lactam **18f** aus, welches bei der Umsetzung mit dem Thiolactam **18b** in Gegenwart von ^{t}BuOK in ^{t}BuOH in hoher Ausbeute zum Kopplungsprodukt **18d** führt [21][99].

In mechanistischer Hinsicht erwies sich die letztgenannte Umsetzung als viel komplexer als die ursprünglich in Betracht gezogene Möglichkeit, wonach das (Iodomethyliden)-lactam **18f** mit seinem *N*-Acyl-iodomethyl-ketimin-Tautomeren im Gleichgewicht stehen und als letzteres das Thiolactam **18b** direkt zu **18d** *S*-alkylieren würde. Eine NMR-spektroskopische Verfolgung der Reaktion offenbarte, dass während der Umsetzung von **18f** mit **18b** sowohl das Disulfid **18c**, als auch das I-freie Methyliden-lactam **6e** in weitgehend stationär bleibenden (kleinen) Mengen auftreten. Wie delikat die diesbezüglichen Verhältnisse tatsächlich sind, wurde auch durch die präparativen Befunde nahegelegt, wonach das hoch substituierte Thiolactam **18b** die oxidative Kopplung mit Bz_2O_2 zu **18d** sehr effizient einging, die entsprechende Umsetzung mit dem unsubstituierten Pyrrolidin-thion hingegen völlig misslang [21]. In auffallendem Gegensatz hierzu, liess sich Pyrrolidin-thion sehr wohl alkylierend mit **18f** zum entsprechend Kopplungsprodukt und dieses weiter zum entsprechenden Vinamidin-Derivat umsetzen. Die deutlich höhere Stabilität von **18c** – und damit die Verfügbarkeit als Kopplungsreagens – im Vergleich zum Disulfid des unsubstitutierten Pyrrolidin-thions dürfte wohl hauptsächlich durch den Einfluss der elektronegativen CN-Gruppe auf das Disulfid-System von **18c** bedingt sein[35]).

2.6. *Corrin-Synthesen* via *(*A → D*)-Ringschluss: Die photochemische (*A/D*-Secocorrin → Corrin*)-Cycloisomerisierung.*

Im Rückblick erscheint dem Autor die Chemie der photochemischen (*A*/*D*-Secocorrin → Corrin)-Cyclosisomerisierung als eigentlicher Höhepunkt der 1960 an der ETH begonnenen und bis 1972 die ETH/Harvard Arbeiten am Vitamin B_{12}-Projekt begleitenden corrinsynthetischen Modelluntersuchungen [13–15][17][19][20][29]. Die Beurteilung bezieht sich auf die Hintergründe des konzeptuellen Entwurfs dieser Ringschluss-Reaktion, auf die Inkaufnahme des besonderen Risikos beim Einstieg in ein Syntheseprojekt, in welchem erst in der allerletzten Stufe einer mehrstufigen Synthese eine bislang unbekannte Ringschluss-Reaktion über Erfolg oder Misserfolg entscheiden würde, hierauf auf die 'Entdeckung', wonach die angezielte präzedenzlose Ringschluss-Reaktion tatsächlich existiert, und schliesslich auf die Tatsache, dass die Reaktion im Zeitraum von nur eineinhalb Jahren (1970–1971) zur 'Kernstufe' einer eigenständigen Variante der Synthese des Vitamins B_{12} werden konnte (vgl. *Kap. 3*). Wie im Zusammenhang mit *Fig. 10* und *11* bereits angedeutet, stand am Ursprung dieser Entwicklung die Vorstellung von einer Corrin- und Vitamin B_{12}-Synthetik, welche von der in der molekularen Struktur des Vitamins verkappt vorliegenden

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34) Die CN-Gruppe als Schutzfunktion einer Enamid-(C=C)-Bindung war erstmals von *Alexander Wick* während seines Postdoktorats im *Woodward*'schen Laboratorium im Zusammenhang mit Arbeiten zur Harvard-Variante der Umwandlung des Ringes *B*- in den Ring-*C*-Vorläufer verwendet worden (*A. Wick*, unveröffentlichter Postdoktorats-Arbeitsbericht, Harvard University 1967).

35) Vgl. z.B. den stabilisierenden Einfluss elektronegativer Substituenten (z.B. der CF_3-Gruppe) auf die Beständigkeit von peroxidischen Bindungen [228].

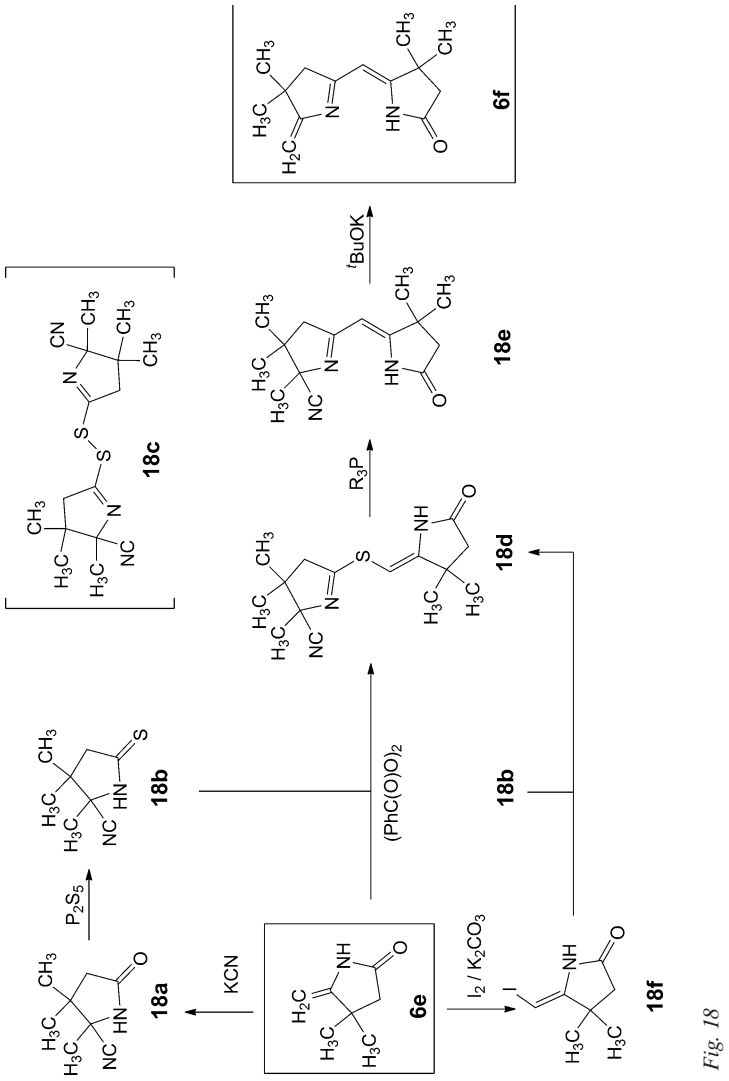
6f
18e
18d
18c
18b
18a
6e
18f
tBuOK
R3P
(PhC(O)O)2
P2S5
KCN
I2 / K2CO3

Fig. 18

Fig. 18. The advent of the 'sulfide contraction' method in 1966 initiated major changes in planning and experimentation not only in the pursuit of the vitamin B_{12} project, but also in ongoing model studies on corrin synthesis. First of all, there was the opportunity, as well as necessity, of exploring a new and more reliable access to the bicyclic lactam **6f**, the well-approved common precursor of the *B*/*C* component in the syntheses of the corrin complexes of the penta-, tetra-, and heptamethyl series. Moreover, the method stirred up new hope and opened new vistas for constructing a corrin ligand from one single precursor, a challenge that originally was triggered by the discovery of the dimerization of that remarkable methylidene lactam **6e** depicted in *Fig. 10*. There was new hope in the sense that the method alluded to possibilities of constructing a tetracyclic *A*/*D*-secocorrinoid ligand system that would have to be prepared, if an idea gaining shape just about that time would have to be followed up by experiments, namely, a corrin synthesis by way of a final corrin ring closure between rings *A* and *D* (*cf. Sect. 2.6*).

The new synthesis of the bicyclic lactam **6f** from two molecules of the single starting material **6e** [14] was not much more than applying the result of the exploratory work done in the B_{12} project as discussed in the context of *Fig. 16*. Yields in each step of the sequence **6e** → **18a** → **18b** → (**18c**) + **6e** → **18d** → **18e** → **6f** were uniformly high [14][98].

In this context, a surprising and, at the same time, instructive observation was made: we were unable to achieve an oxidative coupling of the *unsubstituted* pyrrolidin-2-one with enamide **6e** under a variety of conditions [99], among them those under which the coupling **18b** → (**18c**) + **6e** → **18d** proceeded in 72% yield. The reason for this failure turned out to be the (observed) thermal instability of the disulfide intermediate derived from the unsubstituted pyrrolidine-2-thione, causing its decomposition to be faster than its reaction with **6e**. In sharp contrast, the tetrasubstituted disulfide **18c** was so stable that it could be isolated and stored. We ascribe the relative stability of the latter not primarily to the presence of the six Me substituents, but rather to the electronically stabilizing influence of the (electronegative) CN substituent on the S–S bond[35]).

An alternative coupling pathway developed much later used the iodo derivative **18f** as reaction partner, one which originally was assumed to alkylate a thiolactam partner as its iodomethyl-ketimine tautomer [21]. The coupling with the thiolactam S-atom succeeds in the presence of a strong base, it does so efficiently not only in the substituted series (**18f** + **18b** → **18d**), but – importantly – also with the unsubstituted pyrrolidine-2-thione [21]. Surprisingly, observations made in monitoring the reaction **18f** + **18b** → **18d** indicated the mechanism(s) by which the iodide **18f** couples with thiolactam **18b** being far from straightforward [21] (*cf. Part VI* of this series).

Reaction conditions [98][99]: **6e** → **18a**: KCN, $KHCO_3$, H_2O, r.t.; 90%; **18a** → **18b**: P_2S_5, in benzene, 80°; 82%; **18b** + **6e** → (**18c**) → **18d**: Bz_2O_2, benzene, r.t.; 72%; **18d** → **18e**: Ph_3P, 130°; 84%; **18e** → **6f**: ^{t}BuOK, ^{t}BuOH, 80°; 88%; **6e** → **18f**: I_2, Et_2O, K_2CO_3, r.t.; 87%; **18f** + **18b** → **18d**: ^{t}BuOK, ^{t}BuOH, r.t.; 88%.

Symmetrie Gebrauch machen und sämtliche vier peripheren Ringe des Ligand-Systems aus einem einzigen Ringvorläufer herleiten würde. Zwar hatte die Entwicklung der Sulfid-Kontraktion-Methode diese Vorstellung gedanklich um ein gutes Stück der Realität näher gebracht, doch verblieb – nachdem in einer frühen Modellreihe ein im Grunde konventioneller Versuch im Wesentlichen gescheitert war – nach wie vor die Direktverknüpfung der Ringe *A* und *D* als Haupthindernis der Erkennung einer überzeugenden Synthesestrategie.

Die Überlegungen, die in der ersten Hälfte des Jahres 1967 zum Entschluss führten, den experimentellen Aufwand einer mehrstufigen Modellsynthese in die Frage nach der Existenz der (*A*/*D*-Secocorrin → Corrin)-Cycloisomerisierung zu investieren, fügten sich bezüglich dieser Ringschluss-Reaktion nicht in das Schema der konventionellen Syntheseplanung durch 'retrosynthetische Analyse' ein. Eine retrosynthetische Dissektion der (C–C)-Bindung der Direktverknüpfung zwischen den Ringen *A* und *D* der Corrin-Struktur *würde man eben gerade nicht dergestalt vornehmen*, dass deren Umkehrung einer präzedenzlosen chemischen Reaktion entspricht. Aus diesem Grund sei hier der gedankliche Weg nachgezeichnet, der zur Konzeption dieser alles entscheidenden Ringschluss-Reaktion geführt hatte (*Fig. 19*).

Würde man die dehydrierende Verkopplung zweier Moleküle des monocyclischen Methyliden-lactams **6e** mittels der Methode der Sulfid-Kontraktion, wie sie bei der in *Fig. 18* erläuterten Synthese des bicyclischen Methyliden-lactams **6f** erfolgte, auf die Anknüpfung eines weiteren Ringbausteins **6e** anwenden, so wäre das Produkt das tricyclische Lactam **19a** (*Fig. 19*). Unschwer assoziiert man mit der in dieser Anordnung präsentierten Strukturformel die Ringe *A*, *B* und *C*. Bei nochmaliger Anwendung dieses Aufbaukonzepts auf die Einfügung des Ringes *D* an den Tricyclus **19a** zum Tetracyclus **19b** stiesse man bezüglich möglicher Folgestufen auf eine durch die spezifische Konstitution des Corrin-Systems gesetzte Hürde, denn der durch solche Wiederholung des dehydratisierenden Prozesses der C,C-Verknüpfung sich ergebende Tetracyclus **19c** läge auf der Konstitutions- und Oxidationsstufe eines *Hexahydro*-porphins, er wäre also ein Vertreter des Strukturtyps des *Corphins* [12]. Würde man formal dem Unterschied zwischen den Oxidationsstufen des Corphins und Corrins Rechnung tragen wollen, müsste man bei der Anfügung des Ringes *D* anstelle des Methyliden-lactams **6e** dessen Deoxo-Analogon **19d** als Ring-*D*-Vorläufer einfügen. Doch von dem sich hierbei ergebenden Tetracyclus **19e**, dessen Ring *C* keine funktionelle Gruppe mehr trägt, wäre an sich keine Möglichkeit zu einem weiteren Ringschluss zu erwarten. Die Formel **19e** steht für nichts anderes als ein zwischen den Ringen *A* und *D* offenes *Konstitution-Isomer des Corrins* **19f**. So trivial diese Feststellung auch sein mag, die Frage, zu der sie schliesslich hinführte, war es nicht*:* gäbe es vielleicht die Möglichkeit einer *Isomerisierung* von **19e** zu **19f***?* Es war dies die Frage, die am Ausgangspunkt der Entwicklung des 'neuen' Weges zum Corrin-System stand, dem Weg zur Corrin-Struktur *via* photochemische (*A*/*D*-Secocorrin → Corrin)-Cycloisomerisierung [13–15][17].

Seeing in formula **19e** an *A*/*D*-*seco*-isomer of corrin **19f** may have been trivial, the question as to whether a reaction might exist that would transform one into the other was not. Pondering the issue on a purely formal level led to the following considerations: a constitutional change of type **19e** → **19f** – considered to be sterically assisted by a coordinating metal ion – would be expected to be exothermic: two C–C bonds would be formed on the cost of one C=C bond. Such a process (*Fig. 20*) would formally involve the transfer of the H-atom in **20a** from the CH_2(19) group of ring *D* to the methylidene C-atom at C(1) of ring *A*, thereby creating a (conjugatively stabilized) 1,19-diradical intermediate **20b**, which – if formed – might collapse to the corrin complex **20c**. A helical conformation, imposed on the secocorrinoid ligand by the coordinating metal ion, might posit the ring-*D* CH_2 group directly below (or above – in the enantiomorphic coil; *cf. ent*-**20a**) the methylidene C-atom. Such proximity between

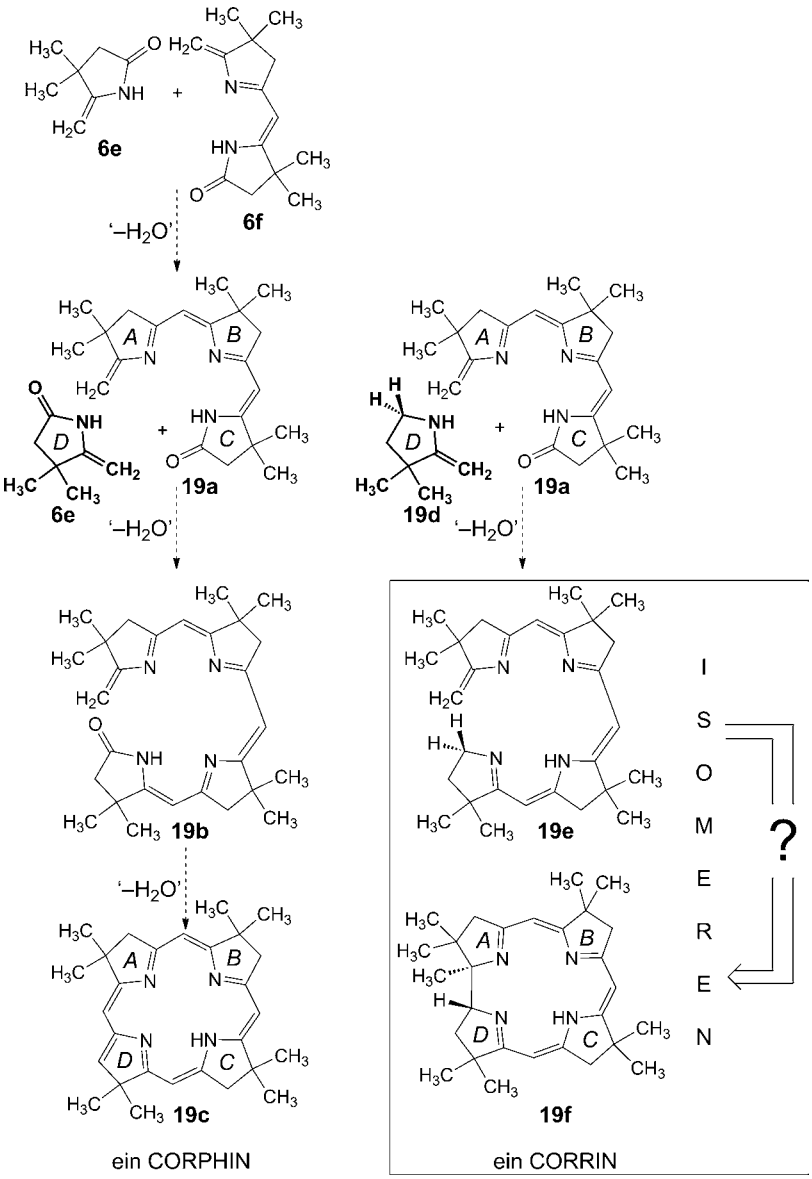

Fig. 19. In retrospect, the author tends to think of the chemistry of the photochemical *A*/*D*-secocorrin → corrin cycloisomerization [13–15][17][19][20][29] as the apogee of the studies on corrins and vitamin B_{12} pursued by his research group at the ETH between 1960 and 1972. While, among all the reactions and methods that were used in these studies, some may have involved chemical novelty to some degree, the photochemical cycloisomerization reaction had no precedence. It solved the problem of constructing the – as originally believed – synthetically most difficult part

of the vitamin B_{12} structure in a way that might be near to an attainable optimum. At the roots of the 'targeted discovery' of this structural transformation had been the 'dream of a synthesis' already referred to in the context of *Figs. 10* and *11*, namely, being able to derive all four of the vitamin's peripheral rings from on single starting material, taking into account the hidden generational symmetry within the vitamin's molecular structure[36]).

The plan to incorporate the constitutional change brought about by the *A*/*D*-secocorrin → corrin cycloisomerization in a synthetic scheme could not come from a retrosynthetic analysis of the conventional type, since the latter would simply not allow for a 'bond dissection' of which the reversal corresponds to an unknown type of reaction. Therefore, an attempt is made here to trace the kind of reasoning that led to the question as to whether a reaction that would lead to such a structural transformation does actually exist (*Fig. 19*).

When it was realized that the *B*/*C* component **6f** can be built from two molecules of the methylidene-lactam **6e** using the 'sulfide contraction' method, it did not require much pondering about whether such an – in essence *dehydrative* – coupling process could be repeated in order to afford a tricyclic chromophore system of type **19a**, the structure of which would be easily seen as representing rings *A*, *B*, and *C* of a corrin, all of them deriving from the same precursor **6e**. Repeating the process still once more would produce the tetracyle **19b**, from which a *dehydrative* ring closure would afford **19c**. This would be a derivative of a ligand system that we had referred to as a *corphin*[37]) in earlier work, a *hexahydro*-porphin, differing from a corrin not only by the size of the macrocycle, but also in its oxidation level. The oxidation level of a corrin ligand corresponds to that of a *decahydro*-porphin. If one were to extend the tricycle **19a** at ring *C* end not with **6e**, but rather with the correspondingly *reduced* ring *D* precursor **19d**, the tetracycle **19e** would result. It was hardly possible to overlook that **19e** happens to be a constitutional A/D-*seco-isomer* of corrin **19f**. While this was, of course, nothing more than a loose play with constitutional formulae, it generated an important question: *Could it be that a chemical reaction exists that would be capable of effecting a conversion of one isomer to the other, capable of accomplishing an* '*isomerization*' *of the* A/D-*secocorrin* **19e** *to the corrin* **19f** *?* This was the question that stood at the outset of the development of the 'new way' to corrins, the one *via* the photochemical *A*/*D*-secocorrin → corrin cycloisomerization [13–15] [17].

a ring-*D* H-atom and the ring-*A* methylidene might be expected to assist the H-transfer if – and this was the 'big' if – such a move would have a chance at all. And finally: if the helical ligand conformation were to persist in the diradical intermediate, the collapse would lead to the *trans*-junction between rings *A* and *D* in the corrin.

It is quite probable that such a formalistic chemical reasoning would have been dismissed as sheer play with chemical formulae, had organic chemistry not gone

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[36]) There were those earlier (and essentially unsuccessful) attempts to construct the *A*/*D* junction of corrin complexes by photochemical decarbonylation of 19-oxo-*A*/*D*-secocorrin- or 19-oxo-*A*/*D*-corrin complexes, as discussed in context with *Fig. 11*. Such a corrin synthesis would also have derived all four rings from one single starting material *i.e.*, the monocyclic ene-lactam **6e**. For a detailed description of the 'decarbonylation approach' of corrin synthesis, see *Part IV* of this series (there Figs. 11 and 12).

[37]) In fact, ligand **19c**, as well as some of its complexes, have been prepared from the secocorphinoid ligand **19b** *via* alkylation of the lactam O-atom and ring closure by imido ester/enamine condensation within corresponding Pd^{II}, Ni^{II}, and Zn^{II} complexes [23]. For the first synthesis of a corphin as the Pd^{II} complex of ligand **19c**, see *Fig. 11* and [12].

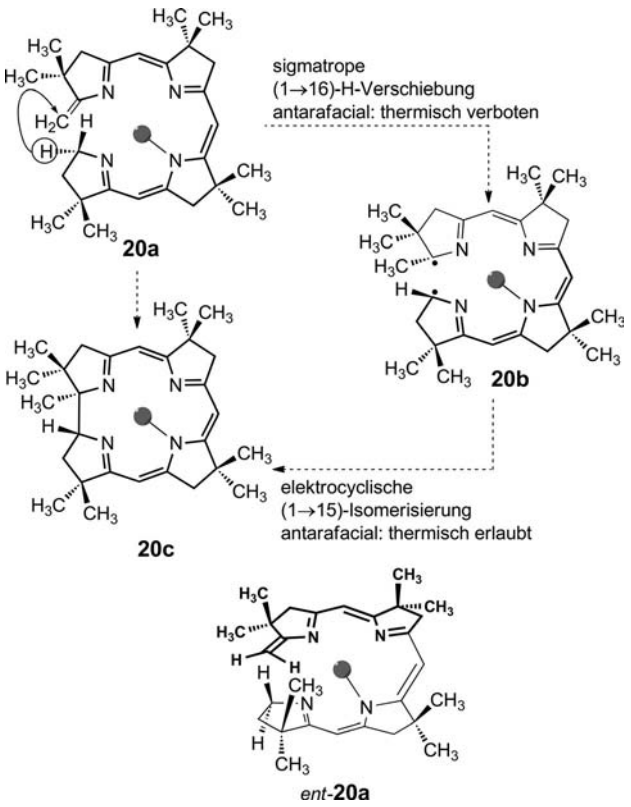

Fig. 20. *Promoting a* 'play with chemical formulae' *and* 'wishful thinking' *to a* 'working hypothesis based on theory' *by recognizing that the two steps of a structure change formally required for bringing about an isomerization of an* A/D-*secocorrin to a corrin would be special cases of reaction types that* Woodward *and* Hoffmann [230] *in the context of their theory of orbital symmetry control of organic reactions had defined as* 'sigmatropic rearrangements' *and electrocyclizations.*

through the *Woodward* and *Hoffmann* (*W–H*) 'revolution' [229] just about that time. Looking at the issue in the light of the 'orbitalistic' view on electrocyclic reactions promoted these ideas from 'wishful thinking' to a serious *hypothesis* based on theory (*Fig. 20*). Actually, not necessarily the orbital symmetry rules as such provided the primary impetus for taking the 'plan' serious and deciding to test it experimentally; crucial for that decision were *Woodward* and *Hoffmann*'s conceptual generalizations [230] on the type of organic reactions that they defined as 'sigmatropic rearrangements' and, among them in particular, sigmatropic $(1 \rightarrow n)$-H shifts. In this view, the move of a H-atom from ring *D* to ring *A* became conceptually a *sigmatropic (1 → 16)-H shift* and, as such, an (admittely exotic) example of a 'known reaction type'[38]). Reassurance and

[38]) At that time, the most prominent example of such a H shift accompanied by a C=C bond shift was the one observed in the chemistry of vitamin D [231].

encouragement came of course also from the *W–H* orbital-symmetry rules. HMO Calculations by *Reinhart Keese*[39]) and *Klaus Müller*[40]) in our laboratory on the two π-systems relevant for the overall process provided the necessary data (*cf.* Fig. 1 in [14]): the symmetry of the half-occupied frontier orbital π_9 of the 16-center-π-system relevant to an antarafacially proceeding sigmatropic $(1 \rightarrow 16)$-H shift was pointing to the prediction 'thermally forbidden', whereas the symmetry of the doubly occupied frontier orbital π_8 relevant to an antarafacial $(\pi \rightarrow \sigma/1 \rightarrow 15)$-collapse of the intermediate 'diradical'[41]) predicted the latter to be 'thermally allowed'. In other words, according to the *W–H* rules the cycloisomerization process would have to be initiated photochemically. The helical conformation of the secocorrinoid ligand in the metal complex would impose antarafaciality in both steps for steric reasons. This would force the configuration of the *A*/*D*-ring junction, formed in the second step, to be *trans*[42]) [14]. However, there still were lingering doubts whether the overall process – if proceeding at all – would really obey these rules, since, after all, the structural complexity of the two nitrogenous π-systems transcended by far the structural boundaries inside which '*reaction control by orbital symmetry*' had been, at that time, secured empirically.

The choice of the model system for testing the *A*/*D*-secocorrin $\rightarrow$ corrin cycloisomerization experimentally was clear: it would have to be a metal complex of the *A*/*D*-secocorrin ligand **21g** of the heptamethyl series (*Fig. 21*), because the $A \rightarrow D$ cycloisomerization would lead to an already known 15-cyanocorrin complex (*cf. Fig. 8*), and as such would be quickly and reliably detectable even in traces, should it turn up in product mixtures of explorative experiments. Starting materials for the synthesis of the model system **21g**, first envisaged as Ni^{II} complex, were the 'old' bicyclic lactam **6f** containing rings *B* and *C* (*cf. Figs. 8* and *18*), the already mentioned thiolactam **18b** as precursor of ring *A* (*Fig. 18*), and the cyano-enamine **21h** as the precursor of ring *D*. Both the oxidative, as well as the alkylative version, of the sulfide contraction method turned out to be efficient in affording the sulfide-bridged tricycle **21b**, either directly, using the (isolated) disulfide derived from **18b** as oxidant, or by *S*-alkylation of **18b** by the iodo-ene-lactam **21a** obtained by iodination of **6f**. The imido-ester **21e**, required for attaching the ring *D* precursor **21h**, was prepared from **21c** *via* its (nicely crystalline) Ag^{I} complex **21d** in which the N-centers were protected against being attacked by the *Meerwein* salt[43]). The tetracycle was isolated as Ni^{II} complex **21f** ($M = Ni^{+}$) perchlorate, from which the target compound, the *A*/*D*-secocorrin complex **21g** ($M = Ni^{+}$) was obtained by base-catalyzed elimination of the CN group in ring *A*.

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[39]) *Reinhart Keese* (research associate ETH, 1.12.1963 – 1.4.1968; *cf.*, *e.g.*, [223])

[40]) *Klaus Müller*, doctorate ETH (on the topic of slow inversion at pyramidal nitrogen), 1.1.1968 – 8.12.1970; *cf.* [94].

[41]) Much later, when non-photochemical variants of the *A*/*D*-secocorrin $\rightarrow$ corrin cycloisomerizations such as the base-catalyzed $(A \rightarrow D)$-cyclization of 19-carboxy- and 19-formyl-*A*/*D*-secocorrinates were realized [31][114], it became clear that the postulated intermediate of the cycloisomerization is to be be viewed not only as a 'diradical', but also as an 'ylide' π-system [28].

[42]) Compare in this context the unsuccessful attempt to generate an 1,19-*cis*-corrin complex *via* an $A \rightarrow B$ corrin ring closure (*cf. Fig. 9*).

[43]) Instructive contrast to the corresponding *O*-alkylation of **6f** in the bicyclic series, where the N-atom is protected against *N*-alkylation by the internal H-bond (*cf. Figs. 7* and *8*).

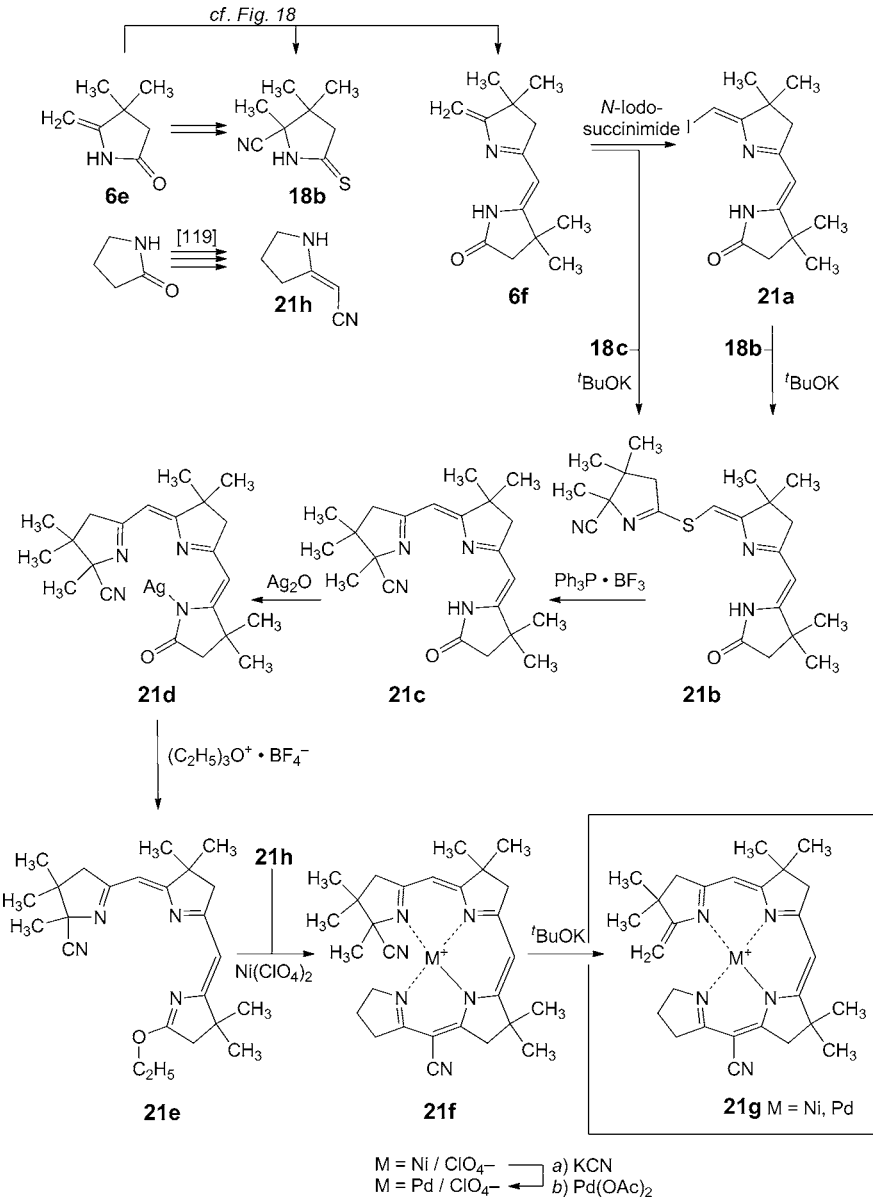

Fig. 21. *Synthesis of Ni^{II}- and Pd^{II}-*A/D-*secocorrin complexes* **21g** *chosen as the first model substrates to test the* A/D-*secocorrin → corrin cycloisomerization.*

Reaction conditions [14][21][86][98][99]: **6f** + **18c** → **21b**: ^{t}BuOK, ^{t}BuOH/benzene, r.t.; 51%; **6f** → **21a**: *N*-iodosuccinimide (NIS), benzene/^{t}BuOH, r.t.; 81%; **21a** + **18b** → **21b**: ^{t}BuOK, ^{t}BuOH/benzene, r.t.; 70%; **21b** → **21c**: Ph_3P, BF_3, benzene, 80°; 82%; **21c** → **21d**: Ag_2O, benzene, r.t.; 95%; **21d** → (**21e**) → **21f** (M = Ni): Et_3O^+/BF_4^-, $EtN(^iPr)_2$, CH_2Cl_2, r.t., → addition of **21h**, r.t., → $Ni(ClO_4)_2$, CH_3CN, EtONa, r.t.;

68%; **21f** (M = Ni) → **21F** (M = H) → **21f** (M = Pd): a) KCN, MeOH, r.t.; b) $(AcO)_2Pd$, CH_2Cl_2, EtOH, EtONa, r.t.; 89%; **21f** (M = Ni) → **21g** (M = Ni): ^{t}BuOK, ^{t}BuOH, 80°; 96%; **21f** (M = Pd) → **21g** (M = Pd): ^{t}BuOK, ^{t}BuOH, 80°; 90%.

The corresponding Pd^{II}-*A*/*D*-secocorrin complex **21g** (M = Pd^+) was obtained from **21f** by decomplexation of the Ni complex by KCN, recomplexation with $Pd(OAc)_2$, and base-catalized elimination of the CN group in ring *A*.

It had been clear from the very beginning that investing in a multi-step synthesis of a model substrate and counting on the success of an unprecedented reaction in the last step would be a risky endeavour. In fact, it took *Yasuji Yamada*[44]), *Dusan Miljkovic*[45]), and *Pius Wehrli* [86] almost two years to accomplish the synthesis outlined in *Figs. 18* and *21* of the *A*/*D*-secocorrinate model structure **21g** (M = Ni). When, in early 1968, *Yamada* carried out his first exploratory experiments on the cycloisomerization of this Ni^{II} complex, we experienced a bitter disappointment (*Fig. 22*): neither irradiation with visible light in CH_2Cl_2 at room temperature, or with UV light in triethyleneglycol at 150° under exclusion of O_2, nor heating the substrate to 200° in the dark for 3 h, led to any discernable formation of a corresponding corrin complex. In view of the possibility that the template effect of Ni^{II} might perhaps not be strong enough to bring the potential reaction centers into sufficiently close contact, *Yamada* subjected the corresponding Pd^{II} complex **21g** (M = Pd) to the same treatment, counting on this metal ion's known tendency to favor square-planar coordination (*cf. Fig. 11*). The result was dramatic*: irradiation of a CH_2Cl_2 solution of this Pd^{II}-*A/D-secocorrin complex with sunlight at room temperature led within hours to the formation of the corresponding corrin complex in spectroscopically almost quantitative yield* (first days in May 1968).

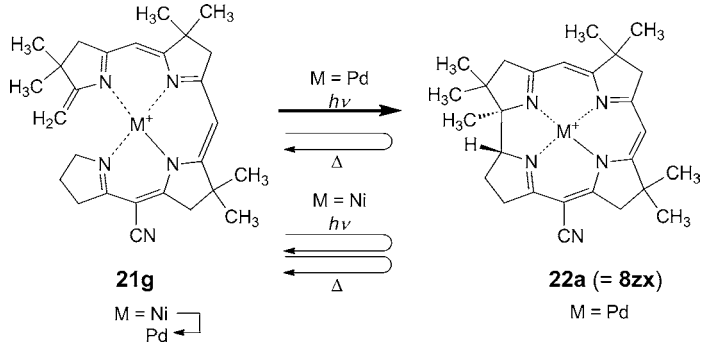

Fig. 22. *First observations of an* A/D-*secocorrin → corrin cycloisomerization (May 1968)*. Whereas the Ni^{II}-*A*/*D*-secocorrinate **21g** (M = Ni) unambiguously failed to undergo the reaction thermally, as well as photochemically, the corresponding Pd^{II} complex smoothly underwent cyclization by irradiation with sunlight in almost quantitative yield to the Pd^{II}-corrinate **22a** (= **8zx**; M = Pd).

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44) *Yasuji Yamada*, postdoctorate ETH, 13.6.1967 – 5.12.1968.
45) *Dusan Miljkovic*, postdoctorate ETH, 1.2.1966 – 31.12.1967.

The identity of the photochemical cycloisomerization product with the corresponding corrin complex was easily recognized spectroscopically, and it was secured eventually by direct comparison of the cycloisomerization product with the Pd^{II} complex **8zx**, a sample of which was specifically prepared for this purpose [98] *via* the alternative pathway to corrins (*cf. Fig. 8*). Notably, but no longer as a surprise: no cyclization of the Pd^{II}-secocorrinate **21g** (M = Pd) could be detected by thermal treatment (250°).

The remarkable contrast in the impact the two transition metal ion Ni^{II} and Pd^{II} had on the photochemical *A*/*D*-secocorrin → corrin cycloisomerization, and the luring challenge to consider a photochemical variant of B_{12} synthesis based on this novel reaction, were calling for a systematic variation of the coordinating metal ion in the model series. After all, we already knew (*cf. Fig. 13*) that Pd^{II} cannot be removed from a corrin complex without destruction of the ligand. In his thesis work started in 1968, *Hans-Jakob Wild* [98] soon found that the question was not whether or not coordination of the *A*/*D*-secocorrin ligand with a specific metal ion is a *requirement* of the reaction, but rather whether or not a given coordinating metal ion *permits* the reaction to occur. A first important observation, the most reassuring for the planned application of the new strategy of corrin synthesis on the vitamin B_{12} problem, was the successful photochemical cycloisomerization of the chloro-Zn^{II} complex of **23a** (M = ZnCl) to the chloro-Zn^{II}-corrin complex **23b** (M = ZnCl; *Fig. 23*). Reassuring was the finding because we already knew that a corrin complex of Zn^{II} can smoothly be converted acidolytically to the corresponding metal-free corrin, and that any other desired metal ion – including Co^{II} – can be introduced into this metal-free corrin ligand (*cf. Figs. 12* and *13*; note that complex **12d** is the chloro-Zn^{II} complex **23b**). *Fig. 23* offers a survey of observations made on the dependence of the cycloisomerization **23a** → **23b** from the nature of the coordinating metal ion: coordination of the *A*/*D*-secocorrin ligand with a second-row transition metal ion such as Co^{III}, Ni^{II}, Cu^{II}, Mn^{II}, and Fe^{II} rules out the photochemical process. Higher-row transition metals such as Pd^{II} and Pt^{II} allow it to proceed, but only relatively slowly, while filled-shell metal ions such as Zn^{II}, Cd^{II}, Mg^{II}, Ca^{II}, Na, and Li support the reaction very efficiently, exclusion of oxygen being a strict requirement. All the secocorrin complexes required for this study were obtained by demetalation of the Ni^{II} complex **21g** (M = Ni) with KCN under carefully controlled conditions, followed by recomplexation of the neutral metal free ligand **23c** (*cf. Part IV*). Most instructive, regarding the role of the coordinating metal ion, is the remarkable and well-characterized case of the labile *A*/*D*-secocorrin lithium 'salt/complex' **23d** which, in an inert solvent, smoothly undergoes cyclization in high yield to the neutral lithium-corrinat **23b** (M = Li). This salt and/or complex of the corrin ligand is extremely sensitive to moisture. Its smooth formation most clearly contradicted the originally pursued working hypothesis (*cf. Fig. 22*), according to which the cycloisomerization requires the support of the coordinating metal ion through a template effect that should be as strong as possible. The alternative view according to which transition metal ions that prevent the cycloisomerization do this by quenching electronically excited states of the secocorrin chromophor system, came up later in the context of spectroscopic and mechanistic investigations carried out at ETH, as well as in other laboratories (*cf. Chapt. 4*).

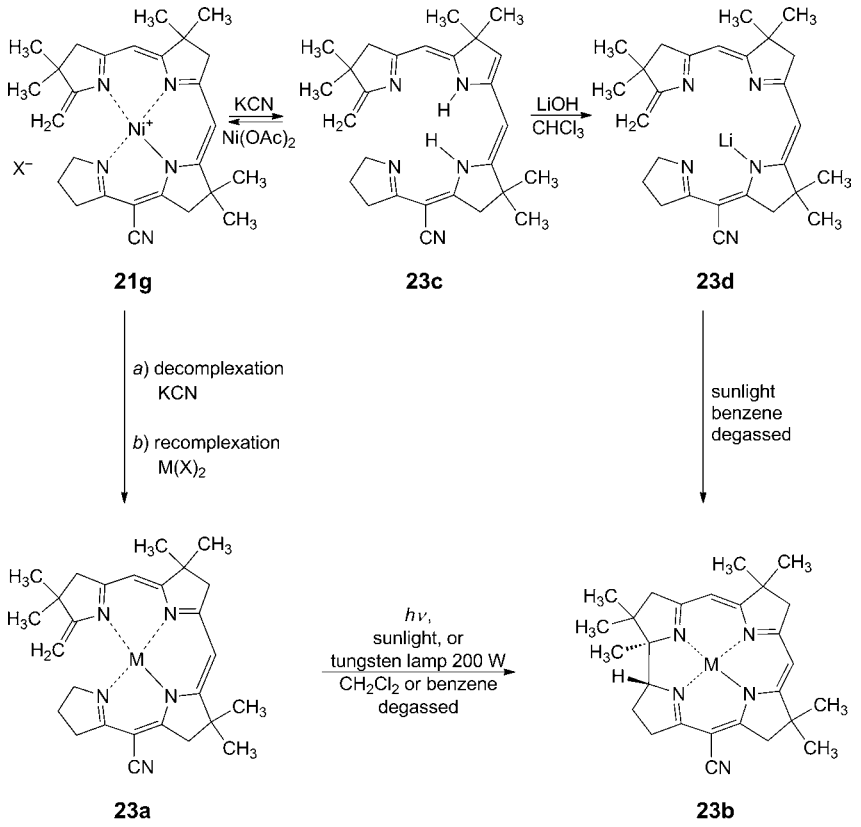

Fig. 23. *Observations made in systematically testing the occurrence* vs. *non-occurrence of the* A/D-*secocorrin* → *corrin cycloisomerization under the influence of visible light as depending on the nature of the coordination-metal ion*. First-row transition-metal ions as coordination centers strictly prevent the occurrence of the reaction, filled-shell metal ions such as Zn, Mg, Ca, Cd, or even Li and Na allow the reaction to proceed smoothly and in high yields, provided atmospheric oxygen is strictly excluded. Pd^{II}- and Pt^{II}-*A*/*D*-secocorrinates also undergo cyclization, yet more slowly, and they were only weakly influenced by the presence of atmospheric oxygen.

Reaction conditions [95][98]: **21g** → **23a**: M = Zn-Cl, Cd-Cl, Mg-Cl, Cu^+: a) KCN, MeOH; b) $M^{II}(ClO_4)_2 \cdot (H_2O)$; c) NaCl, H_2O (M = Zn: 89%, Cd: 70%, Mg: 74%, Cu: 74%); M = Mn-Cl: a) KCN, MeOH; b) $MnCl_2$; 71%; M = Fe-Cl: a) KCN, MeOH, N_2 → free ligand **23c** isolated; b) 'bis-tetraphenyl-arsenium-tetrachloro-ferrate(II)' [152], $CHCl_3$, Ar; 82%; M = Ca-OH: a) KCN; b) $Ca(ClO_4)_2 \cdot$ hydrate, MeOH (not isolated, decomposes with NaCl/H_2O); M = Na: a) KCN, MeOH, N_2; b) *N*-bis(trimethylsilyl)amide, degassed benzene, N_2 (not isolated); **21g** → **23c**: KCN, MeOH, Ar, r.t.; 85%; **23c** → **21g**: Ni^{II}-diacetate, MeCN, N_2, r.t.; 95%; **23c** → **23d**: pulverized LiOH,

$CHCl_3$, Ar, 50°, in the dark; 59%; **21f** (M = Ni^+) → **21f** (M = H) → **21f** (M = Pt^+) → **23a** (M = Pt^+): a) KCN, MeOH, N_2; 98%; b) $Pt(Cl)_4$ $(NH_4)_2$, EtOH, 70°, N_2; 55%; c) ^{t}BuOK, ^{t}BuOH, N_2, reflux; 88%. For the preparation of the Pd-corrinate **23a** (M = Pd), see *Fig. 21.* **23a** → **23b**: M = Pd^+: sunlight, CH_2Cl_2, N_2, r.t.; 90%; M = Zn-Cl, Cd-Cl, Mg-Cl: *hν* (W lamp, 200 W), degassed benzene, Ar, *ca.* 30° (Zn: 89%; Cd: 91%; Mg: 96%); M = Pt^+: sunlight, CH_2Cl_2, N_2, r.t.; 92%; M = Ca-OH: → **23b** (not isolated): *hν* (W lamp, 200 W), degassed CH_2Cl_2, *ca.* 30°; M = Na: → **23b** (not isolated): *hν* (W lamp, 200 W), degassed benzene, *ca.* 30°; **23d** → **23b** M = Li: sunlight, degassed benzene, Ar, r.t.; 88%.

2.7. *Corrin Synthesis* via A → D *Ring Closure: The 'Pacemaker' Model Synthesis for the Photochemical Variant of the B_{12} Synthesis. The* BC + D + A → ABCD *Strategy of Corrin-Chromophor Construction.* Access to the corrin system *via A*/*D*-secocorrin → corrin cycloisomerization – after 1968 no longer a fiction, but fact – quite naturally had a major impact on the ETH group regarding its collaboration with the Harvard group. First of all, the conceptual and constitutional simplicity of the new approach – a strategy that would make the demanding task of constructing an *A*/*D* component as central intermediate of a corrin synthesis dispensible – was called for a reorientation in the ongoing collaborative work, as far as the ETH group was concerned. The final 'attack' on a vitamin B_{12} synthesis *via* a photochemical *A*/*D*-secocorrin → corrin cycloisomerization was launched at the ETH towards the end of 1969 (*cf. Chapt. 3*). In parallel to that effort, still another model corrin synthesis was started that was intended to end up in the photochemical *A* → *D* ring closure also, yet to function as a 'pacemaker synthesis', one that would pave the way for the construction of the *A*/*D*-secocorrin chromophor in the natural series by a *B*/*C* + *D* + *A* → *ABCD* strategy, a sequence of joining the four rings of the *A*/*D*-secocorrin chromophore that had not been used thus far. The synthesis would start with the already known methylidene-protected bicyclic lactam **18e**, to which now first ring *D*, and then ring *A* would be linked, and finally the corrin ring should be closed between rings *A* and *D* (*Fig. 24*). What was hoped for by 'paving the way' was to provide the spectral UV/VIS data of the chromophore systems of the intermediates along this pathway. Such data would assist the recognition of the corresponding chromophore systems in the more complex natural series, where the intermediates in each step might be formed as mixtures of side-chain diastereoisomers and, therefore, their constitutions difficult to ascertain, whereas constitutional assignments by NMR spectroscopy in a model system with only four geminal dimethyl groups at the periphery would be unambiguous. What *Brian Place*[46]) had started toward the end of 1969, *John Gleason*[47]) accomplished in early 1971 (*Fig. 24*), closely parallel to *Walter Fuhrer*'s [102] corresponding accomplishment in the natural series (see below, Chapter 3).

While the attachment of the ring *D* precursor to the *B*/*C* intermediate in the natural series was to be achieved by sulfide contraction *via* alkylative coupling [102], in the pacemaker synthesis it was simply accomplished by imido-ester/enamine condensation

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[46]) *Brian Place*, postdoctorate ETH, 1.10.1969 – 30.9.1970.

[47]) *John Gleason*, postdoctorate ETH, 20.8.1970 – 31.5.1971.

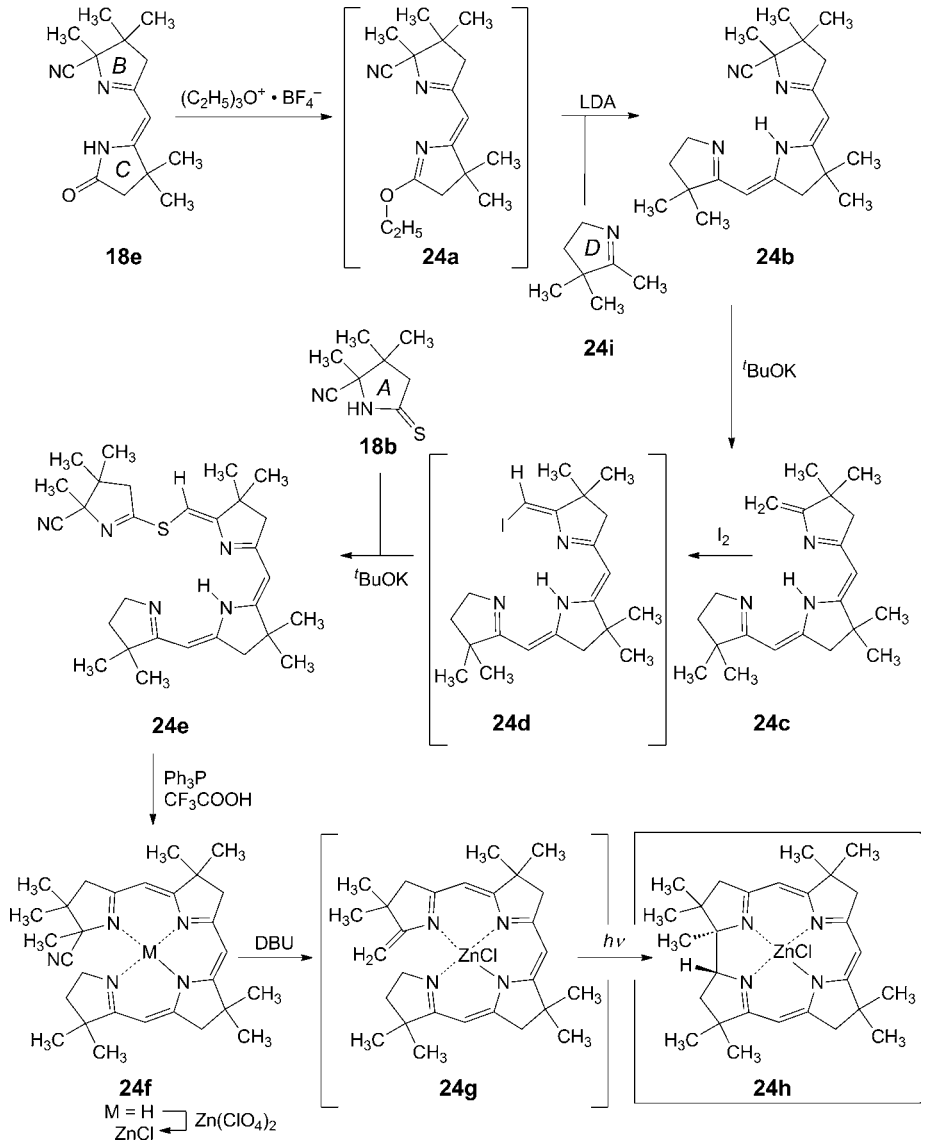

Fig. 24. *Another model corrin synthesis following a* B/C + D + A → ABCD *strategy of secocorrin-chromophore construction serving as 'pacemaker' for the photochemical variant of* B_{12} *synthesis.*

Reaction conditions: **18e** → (**24a**) → **24b**: $Et_3O^+ \cdot BF_4^-$ in CH_2Cl_2, $MeCH_2ONa$ → + (**24i** + $(Me_2CH)_2NLi$ in Et_2O), r.t.; 51% **24b**, besides 31% **18e**; **24b** → **24c**: ^{t}BuOK, ^{t}BuOH, r.t.; 90%, 41%; **24c** → (**24d**) → **24e**: ^{t}BuOK in ^{t}BuOH, + I_2 in benzene + **18b**, r.t.; 38%; **24b** → (**24c** → **24d** → **24e**) → **24f** (M = H): ^{t}BuOK, ^{t}BuOH, r.t., → NIS, benzene, → + **18b**, ^{t}BuOK, ^{t}BuOH, → Ph_3P, CF_3COOH, benzene, 50°; 23% (overall);

24f (M = H) → **24f** (M = ZnCl): $Zn(ClO_4)_2 \cdot 6$ DMF, $EtN(^iPr)_2$, MeOH, benzene; 80%; **24f** (M = H) → **24f** (M = CdCl): $Cd(ClO_4)_2$, $EtN(^iPr)_2$, MeOH/benzene; 68%; **24f** (M = ZnCl) → (**24g**) → **24h**: 1,8-diazabicycloundec-7-ene (DBU), sulfolane, 80°, → *hν* (visible), benzene, under Ar; 65% (spectroscopically), 54% (crystals).

24a + **24i** (as Li-salt) → **24b**[48]). Crucial steps in the synthesis were the coupling of the iodomethylidene tricycle **24d** – prepared *in situ* from **24c** with I_2 – with the protected ring-*A* thiolactam **18b**. The contraction step **24e** → **24f** was brought about with Ph_3P in the presence of CF_3COOH, affording the methylidene-protected *A*/*D*-secocorrin ligand **24f** (M = H), isolated in crystalline form. For preparative purposes, the sequence **24b** → (**24c** → **24d** → **24e**) → **24f** (M = H) was eventually carried out without isolation of intermediates. Deprotection of the methylidene C=C bond in the Zn complex **24f** (M = ZnCl) with DBU and – without isolation of **24g** – irradiation with visible light, afforded the target compound chloro-Zn^{II}-1,2,2,7,7,12,12,17,17-nonamethylcorrinate **24h**.

3. The Final Phase of the Harvard/ETH Collaboration on the Synthesis of Vitamin B_{12}[49])**.** – 3.1. *Background.* The collaboration of the research groups of Harvard and ETH on the synthesis of vitamin B_{12} in the years 1965 – 1972 was personally, as well as chemically, straightforward at its beginning, yet rather intricate at its end. While the ETH synthesis of the first model corrin in 1964 [4][6] had acted as a major catalyst for both groups to enter the collaboration, the second model corrin synthesis, the one published by the ETH group in 1969 [14] may have caused the intricacies of the final phase. In May 1968, when that second model study had reached its goal with the 'targeted discovery' of the photochemical *A*/*D*-secocorrin → corrin cycloisomerization, work at Harvard and at the ETH on the *A*/*D* + *B*/*C* strategy of vitamin B_{12} synthesis had been ongoing already for about seven years, the last three of them collaboratively. The two groups had started their work on vitamin B_{12} independently, at Harvard in August 1961, and at the ETH in September1960, about half a year after the model study in corrin synthesis had been initiated. By 1965, the group at the ETH had accomplished the synthesis of a ring *B* precursor of the natural series in the form of both enantiomers and was struggling with the construction of the vinamidine junction between ring *B* and (a close model of) ring *C*, a task that turned out to be far from straightforward. At

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[48]) The ring *D* precursor **24i** was prepared from 4,4-dimethyl-5-oxohexanenitrile [232] according to a procedure developed by *Heinz Gschwend* at Harvard. The preparation included ketalization with ethylene glycol, hydrolysis of the CN to the primary amide group, *Hoffmann* degradation to a primary NH_2 group, hydrolysis of ketal group, and thermal cyclization to the ketimine **24i**. *Gschwend* had prepared the compound in model studies for the *D* → C coupling step of the *A*/*D* + *B*/*C* variant of B_{12} synthesis. In the same context, the *C*-cyano-enamine derivative of **24i** had been prepared at the ETH from the ring precursor **6e** [93] (see also Figs. 17 and 16 in *Part II* of this series); however, its conversion to **24i** was not investigated.

[49]) For an earlier overview of the Harvard/ETH collaboration on the synthesis of vitamin B_{12} by the author, see [74], and for a facsimile reproduction of the handouts of a lecture series on both variants of the synthesis of vitamin B_{12}, distributed by the author at ETH in the summer semester 1973, see [75].

Harvard, in 1964, the group was forced to make its first halt after a fulminant take-off towards the synthesis of an *A*/*D* component with its direct junction between rings *A* and *D* [209b]. At that time, the direct junction between rings *A* and *D* had to be considered as the B_{12} molecule's center of constitutional and configurational complexity. The halt was enforced by *Subra Ranganathan*'s legendary observations of an unexpected stereochemical course of a central reaction step in the construction of the *A*/*D* component, a course that was unexpected on the basis of conventional steric considerations. According to *Woodward* [184], the experimental and interpretational analysis of this impediment to progress along the originally planned path of the synthesis was part of the events that triggered the orbital-symmetry revolution. The impact those observations had on the B_{12} project was that *Woodward*, in the course of the year 1965, changed the original strategy of a linear synthesis of the *A*/*D* component to a strategy of convergent construction involving a ring *D* precursor derived from (−)-campher.

By that time, both *Woodward* and the author had a rather realistic view on what it would mean to deal with all the problems on the way to a chemical synthesis of vitamin B_{12}. Interestingly, the chemistry which the two groups had thus far accomplished happened to be perfectly complementary: Harvard had been focusing on the stereochemically demanding *A*/*D* part of B_{12}'s corrin ligand, and the ETH on the *B*/*C* part containing the vinylogous amidine bridge between the two rings, the characteristic structural element of the B_{12}-molecule's corrin chromophor. For the author, it was the time when the task lying ahead appeared as going to be 'just an extension and application' of the strategy and methodology of the model corrin synthesis of 1964 to a 'more complicated' target structure, a chemically naive view, and one that eventually turned out to be utterly wrong. For *Woodward*, it was the time when the exploration of the consequences of orbital symmetry for organic chemistry must have raged his mind, and this coinciding with being engaged in a synthetic project more complex than any he had tackled before. Under such circumstances, joining forces seemed the most reasonable thing to do. The program seemed straightforward enough: Harvard will synthesize the *A*/*D* part of the B_{12} molecule, ETH will make the *B*/*C* component. Once these building blocks will be available, coupling them – first between rings *C* and *D*, and then closing the corrin ring between rings *A* and *B*, just as it had been done before in the model series – will be a joint effort to be accomplished collaboratively by both research groups. Starting materials and intermediates, as well as information about failures and successes, will be freely exchanged. The decision to collaborate was sheer pragmatism, on both sides, though perhaps not one exclusively of chemical nature, but rather one with a psychological component also: at the end, there would be two winners and no loser. Needless to say that the vast asymmetry in scientific status, achievement, experience, and age between the two partners made the agreement an adventurous endeavor for the junior partner, at the chemical, as well as the personal level. He remembers how his former teacher and later colleague *Vladimir Prelog* used to quote in this context the old Croatien proverb: '*The newly born calve is not afraid of the tiger*', while his old mentor *Leopold Ruzicka* expressed fatherly warnings.

The stage that the collaborative B_{12} project had reached in summer 1968 is recorded in *Woodward*'s lecture [208a] at the '5th International Symposium on the Chemistry of Natural Products' in London (July 8 – 13, 1968). The Harvard group had accomplished

the synthesis of what constituted a model of the *A*/*D* component, a model in the sense that all its carboxy functions were present as methyl-ester groups (*cf. Fig. 25*; **25a**, R = $COOCH_3$), whereas in the real *A*/*D* component the carboxy function of the propanoic acid side chain at ring *D* would have to be *differentiated* from all the others, *e.g.*, as in **25a** (R = CN). The final version of this model *A*/*D* component was to serve as a vehicle for exploring the coupling with the ETH *B*/*C* component by the method of 'sulfide contraction'. That new method of creating C–C bonds had emerged during 1966 as the resolution of the struggle of joining the precursors of rings *B* and (at first, a close model of) ring *C* (*cf. Sect. 2.5*, *Fig. 16*). Meanwhile, the Harvard group had developed a synthesis of the ring-*C* precursor from (+)-camphor (see below), rendering large amounts of this building block. In early 1967, the *B*/*C* component and the Harvard model *A*/*D* component were ready to be coupled together. At the time of *Woodward*'s lecture, the first step towards that goal, the intermolecular alkylative coupling to form the sulfide bridge between rings *D* and *C* of this *A*/*D* model **25a** (R = $COOCH_3$) and the *B*/*C* component **25b**, had already been accomplished, and preliminary success in the contraction step also had been achieved, yet both groups were struggling with difficulties that were due to the ease by which the sulfide-bridge intermediate would tautomerize to non-contracting isomers.

As discussed at some length in *Sect. 2.6*, the prospect of a new type of corrin synthesis that would culminate in a final corrin ring closure between rings *A* and *D*, and thereby create the corrin ring's *A*/*D* junction in a completely novel way was emerging around 1966. The model study on this alternative corrin synthesis was launched late in the fall of that year, culminating in spring 1968 with *Yasuji Yamada*'*s* successful accomplishment of the photochemical *A* → *D* ring closure of a Pd^{II}-*A*/*D*-secocorrin complex [13–15]. This 'targeted discovery' of the photochemical *A*/*D*-secocorrin → corrin cyclosomerization in the model series just a few months before *Woodward*'s lecture in London could not but have an incisive influence on the ETH group regarding its collaboration with the group at Harvard on the original *A* → *B* ring closure strategy. The success of the second corrin model synthesis opened the prospects for a variant of the B_{12} synthesis that might be dramatically simpler than the one under way in the two laboratories since the early 1960s.

At first, nothing changed with regard to the ETH group's involvement in the collaborative project. The transatlantic exchange of samples of *B*/*C* and (undifferentiated) *A*/*D* components for the pursuit of the original *A* → *B* ring-closure strategy in both laboratories continued, whereby – as *Woodward*'s progress report [208b] in his Riga lecture in 1970 documents (see below) – the contributions of the ETH group were by no means fading [13][15][17]. On the other hand, beginning Ph.D. students of the

Fig. 25. *The final steps of two pathways to vitamin* B_{12}*: closing the corrin ring* via A → B *imido thioester/enamine condensation* (the Harvard/ETH variant [13][17][97][103][208]) *and closing the corrin ring by the light-induced* A/D-*secocorrin* → *cyclosisomerization* (the 'photochemical *A* → *D* variant' [19][20][24][29][75]). The scheme depicts the peripheral propanoic acid side chains at rings *A*, *B*, and *C* in the natural 3α,8α,13α-configuration throughout. In reality, mixtures of corresponding diastereoisomers were formed, which had to be separated by HPLC for the purpose of individual characterization and identification.

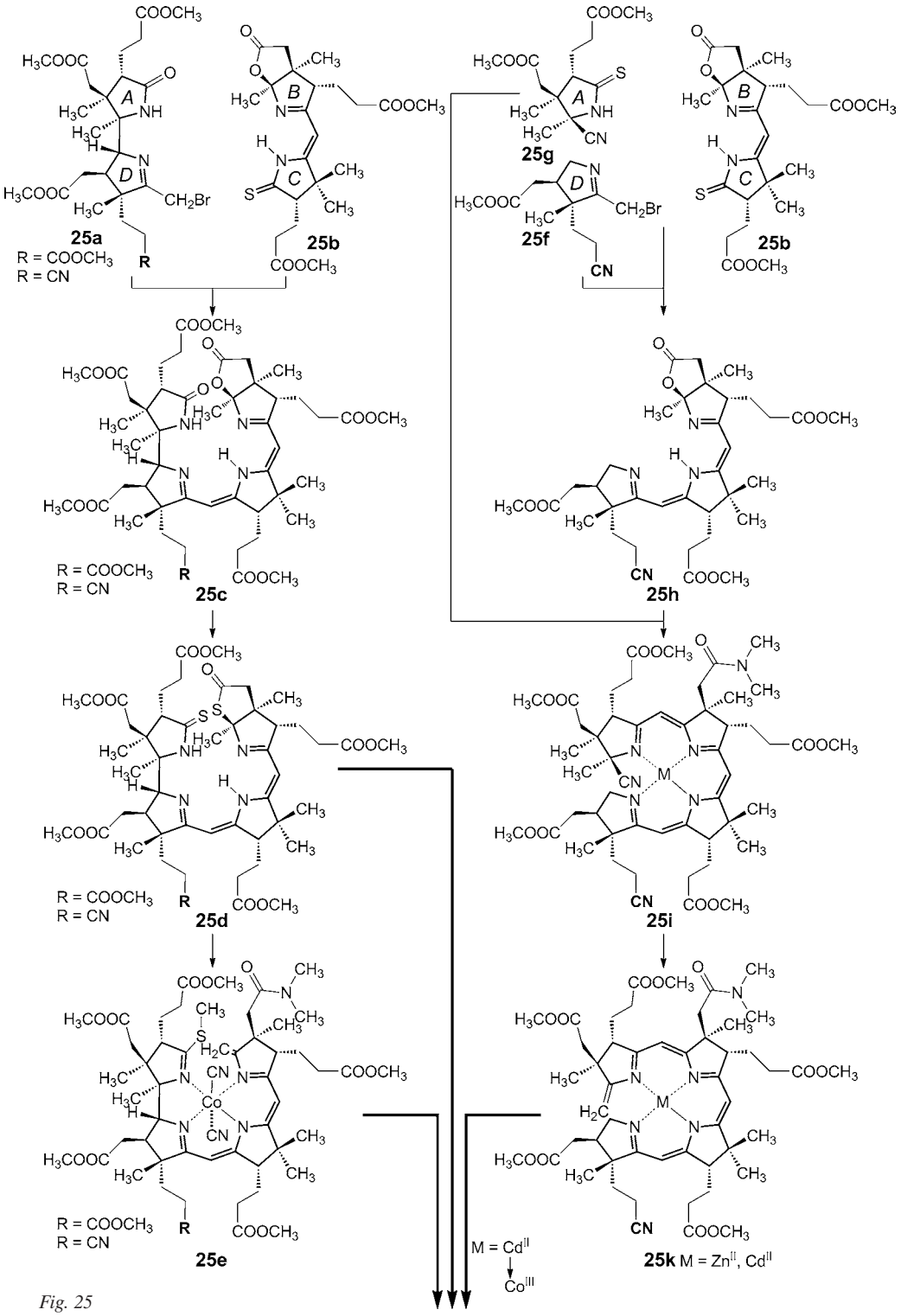
25a
R = COOCH3
R = CN
25b
25g
25f
CN
25b
25c
R = COOCH3
R = CN
25h
25d
R = COOCH3
R = CN
25i
25e
R = COOCH3
R = CN
M = Cd^II
Co^III
25k M = Zn^II, Cd^II

Fig. 25

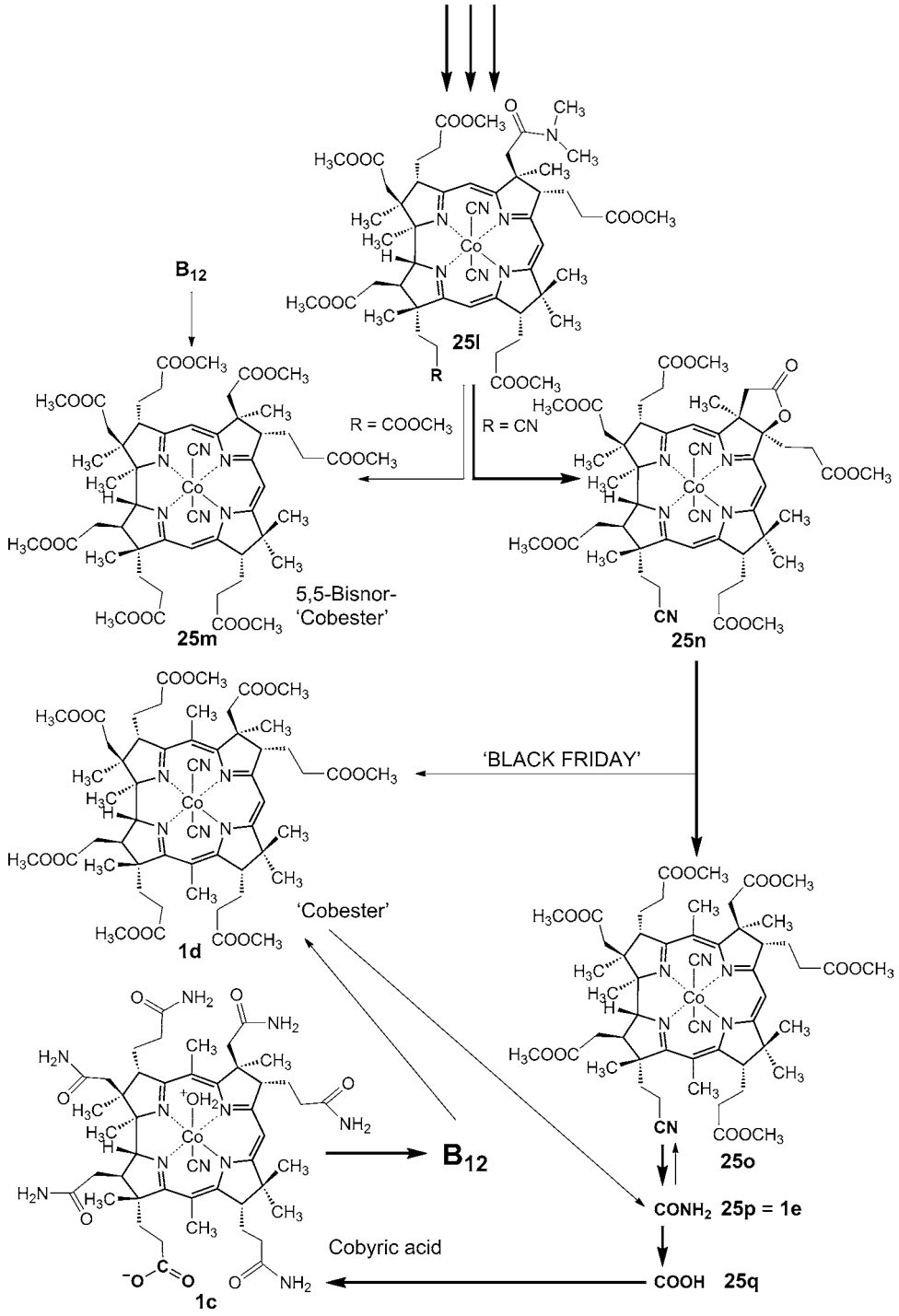
B12
25l
R
R = COOCH3
R = CN
5,5-Bisnor-
'Cobester'
25m
25n
'BLACK FRIDAY'
'Cobester'
1d
25o
CONH2 25p = 1e
COOH 25q
Cobyric acid
B12
1c

Fig. 25 (cont.)

caliber of a *Walter Fuhrer* and of a *Hans Maag*, who joined the ETH group in November 1969, were assigned to explore the pathway toward the photochemical variant of B_{12} synthesis. At that time, there would have been no need anyway to participate the two newcomers in the original project, because the task of the Harvard group to modify their synthesis of the 'model *A*/*D* component' in order to obtain the f-propanoic-acid carboxy function differentiated from all other carboxy functions present in the B_{12} molecule took more time than expected. The differentiated *A*/*D* component that was required to move ahead towards cobyric acid by the *A*/*D* + *B*/*C* strategy did not become available before spring 1971. In retrospect, the author cannot but admit that, with focusing on the challenge of an alternative B_{12} synthesis that would solve the central *A*/*D* problem in an unprecedented and dramatically simplified way, a distinct element of competitiveness was sneaking into the ETH group. But – so the author's assessment at that time – at Harvard such a challenge would hardly have been handled differently, had it come up there.

The collaboration of *Woodward* and the author's research groups on the synthesis of vitamin B_{12} between 1965 and 1972 is documented in lectures the two protagonists had delivered at various occasions [11][13][17][19] [24][29][208a – c], but there is no final publication by *Woodward* and the author in which they together would have described their joint achievement of 1972, namely, the (formal) total synthesis of vitamin B_{12} *via* two different, yet conceptually and methodically entangled pathways, no joint publication in which they would have specified the respective contributions of the two research groups in a way mutually agreed upon. Much of the secondary literature on the Harvard/ETH syntheses of vitamin B_{12} over the last 40 years has basically been swayed by the lecture '*The Total Synthesis of Vitamin* B_{12}' *Woodward* gave at the IUPAC conference in New Delhi in February 1972 [208c]. The author may be forgiven for summarizing here – after four decades – in some detail the contributions of the ETH group in the final phase of the collaborative B_{12} project and describing them as he remembers and sees them in retrospect, and as they are documented in the Ph.D. theses of his former students [80 – 82][87][89][91 – 93][97][102][103][107] (*cf. Footnote 65*).

3.2. *The Final Phase.* – Reviewing the final phase of the collaboration may be divided into three distinct periods, each of them is documented in a published lecture: *Woodward*'s lecture in Riga at the IUPAC Conference on the Chemistry of Natural Products in June 1970 [208b], the lecture entitled '*Studies on Organic Synthesis*' the author presented at the 23rd IUPAC Congress of *Pure and Applied Chemistry* in Boston in July 1971 [19][50]) and, finally, and as already mentioned, the lecture '*Total Synthesis of Vitamin* B_{12}' of *Woodward* at the IUPAC Conference on the 'Chemistry of Natural Products' in New Delhi in February 1972 [208c]. Earlier parts of the final phase are documented in the author's lecture at the *Welch* Foundation Conference (November. 1968) [13], as well as in his *Centenary Lecture* (November 1969) [17]. The photochemical approach to vitamin B_{12} was the topic of the author's lecture in

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[50]) The text of the author's Boston lecture is now accessible in the internet under *ETH e-collection*, A. Eschenmoser '*Studies in Organic Synthesis*', 1971, http://dx.doi.org/10.3929/ethz-a-010165162. The lecture *Woodward* delivered in Boston did not appear in print. However, there exists a tape of *Woodward*'s Boston lecture of which the author has a transcript, including copies of the slides.

Boston [19][50]), and the final accomplishment of this variant of vitamin B_{12} synthesis was announced in Zurich at the Spring Meeting of the *Swiss Chemical Society* in April 1972 in two short presentations that were complementary and presented by *Walter Fuhrer* and *Hans Maag* [20].

3.2.1. *Riga (June 21–27, 1970)*. After *Woodward*'s lecture in London, the battle for the $C \rightarrow D$ sulfide contraction step **25a** + **25b** → **25c** ($R = COOCH_3$) in the undifferentiated series was going on in both laboratories. Before, extensive earlier attempts at the ETH, as well as at Harvard, to join simplified ring-*D* models of potential Harvard *A*/*D* components with the *B*/*C* component by way of imido ester or imidothioester/enamine condensation had been discouraging [13][17][93], as were attempts to bring the ring-*D* β-amino-enone group of a first version of the *A*/*D* component to react with the (highly reactive) imido-ester group of the *B*/*C* component. It had become clear that the critical coupling between the rings *C* and *D* required the reaction to be 'intramolecularized', as the coupling between rings *B* and *C* had been before. The Harvard group had, therefore, re-directed the synthesis of an *A*/*D* component towards the structure **25a** (R = COOMe) that was constitutionally adapted to be joined with the *B*/*C* component **25b** by 'sulfide contraction *via* alkylative coupling', a variant of the oxidative version. This variant had been independently explored in model experiments in both laboratories, and at the ETH the method had been developed to a general method for the construction of β-dicarbonyl systems [16][96].

Samples of the *B*/*C* component and undifferentiated *A*/*D* component were now regularly crossing the Atlantic from East to West and *vice versa*, and information on successes and failures was exchanged in uncounted transatlantic phone calls. What also crossed the Atlantic from East to West were samples of the ring *B* precursor, the model *B*/*C* component, and the model dicyano-Co^{III} complex of the *A*/*B*-secocorrin of the heptamethyl series. Besides the Harvard *A*/*D* component, large supplies of the ring-*C* precursor went from West to East; they were prepared at Harvard from (+)-camphor *via* a route patterned after the ring *C*-synthesis of *J. W. Cornforth* and *Andrew Pelter* in 1961 *(cf. Caption* to *Fig. 2* and [178][179][51]). Originally, the ETH strategy for the synthesis of the *B*/*C* component was to produce the ring-*C* precursor from the ring-*B* precursor by replacing a carboxy group of the latter by H-atom. *Paul Dubs* in his thesis work [92] accomplished such a conversion; it actually served the purpose of correlating the absolute configuration of the synthetic *B*/*C* series with that of an ozonolysis product of vitamin B_{12}, but was not efficient enough to become a preparative source of the large quantities of ring-*C* precursor needed for producing the *B*/*C* component for two laboratories. When *Alexander Wick* had left the ETH to become a postdoc at Harvard (October 1965), *Woodward* also assigned him to work on the problem of converting ring *B* (from ETH) to ring *C*, and *Wick* succeeded at about the same time as *Dubs* did. The method developed at Harvard gave better yields, but was also not efficient enough. In the end, Harvard's preparation of the ring-*C* precursor from (+)-camphor by the (modified) *Cornforth–Pelter* method was in fact the only practical option.

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[51]) According to a private communication of *J. W. Cornforth* to the author (letter of April 16, 1984), it was *Andrew Pelter* who spotted the critical report in the old terpene literature that triggered the *Cornforth–Pelter* synthesis of ring *C*.

Whereas the primary coupling step to the sulfide bridge on the way to **25c** (R = $COOCH_3$) had presented no difficulty, the contraction step posed problems. These were due to the propensity of the labile imido-thioester group to tautomerize into more stable, non-contracting isomers. While the ETH group – directed by observations made in their model studies – arrived at a somewhat exotic and not too reliable contraction procedure (complexation with methylmercury isopropoxide, followed by treatment with Ph_3P/BF_3), it was the Harvard group that eventually prevailed by finding – not the least as the result of an incisive reaction analysis by *Yoshito Kishi* [208b] – efficient and reliable conditions for this critical step (acid-catalyzed isomerization of the primary coupling product to one of the endocyclic imido-thioester tautomers, followed by treatment with tris(2-cyanoethyl)phosphine in sulfolane in the presence of CF_3COOH).

While the optimal reaction conditions for joining rings *D* and *C* by sulfide contraction were found at Harvard, it was at the ETH that *Peter Schneider* was ahead in the developing the follow-up steps, joining rings *A* and *B* to form the corrin ring, *i.e.*, **25c** → **25d** → **25l** (R = COOMe). Not less than three versions of *A* → *B* secocorrin → corrin ring closures had been worked out in the model series at the ETH before: the first by imino-ester/enamine condensation, the second by imido thioester/enamine condensation, both within a Co^{III} complex [6][13][17], and finally the one within a Zn^{II} complex by sulfide contraction [9]. The first of these required a strong base (^{t}BuOK) above room temperature, and, therefore, its application seemed forbidden in the natural series with all its methyl-ester groups. For this reason, the model studies had been extended to the more reactive imido thioester derivative. In this model substrate, the *A* → *B* ring closure could be achieved by treatment with a tertiary amine at enhanced temperature, or even by sheer thermolysis [13][96]. The mildest, though most complex, version of all, requiring neither base nor heating, was the one *via* sulfide contraction within a Zn complex, a method that allowed the preparation of metal-free corrinium salts which could be easily converted into the Co^{III} complex [9][88].

In first attempts to achieve an *A* → *B* ring closure in the (undifferentiated) natural series, *Fritz Karrer*[52]) at the ETH spent his postdoctoral year (1968) trying to reach this goal *via* a thermally induced imido-thioester/enamine condensation, starting from the ring *A* thiolactam/ring *B* thiolactone **25d** (R = COOMe) prepared from the corresponding lactam/lactone **25c** by treatment with P_2S_5, proceeding by conversion of the thiolactam group of ring *A* to a imido-thioester group and, finally, exposing the methylidene group at ring *B* by opening the thiolactone ring. He ran into serious difficulties, not the least because the task of opening the thiolactone ring and exposing the methylidene C=C bond by treatment with base turned out to present a major hurdle, the C=C bond tending to isomerize irreversibly from the exocyclic to an endocyclic position with great ease.

Dealing with the *A* → *B* ring-closure problem using the sulfide contraction method with the Zn complex, departing from either the ring-*A* thiolactam/ring-*B* lactone or the corresponding thiolactam/thiolactone, was the topic of *Peter Schneider*'s thesis work [97]. The breakthrough came with the observation that treatment the Zn complex of **25d** with Me_2NH under carefully controlled conditions opened the thiolactone ring,

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[52]) *Fritz Karrer*, postdoctorate ETH, 1.1.1968 – 28.2.1969

affording the corresponding *N*,*N*-dimethylamide group, and, in addition, exposed the methylidene group at ring *B* essentially without any isomerization of the labile C=C bond. Catching the latter by treatment with iodine resulted in immediate coupling with the ring-*A* thiolactam S-atom. Contraction of the sulfide bridge (Ph_3P, CF_3COOH), followed by re-complexation with Zn, gave the Zn^{II}-corrin complex which – by exchange of the metal ion by $Co^{II\rightarrow III}$ – afforded the dicyano-Co^{III} complex of hexamethyl-5,15-dinorcobyrinate-c-*N*,*N*-dimethyl-amide **25l** (R = COOMe) [17][97]. Selective conversion of the *N*,*N*-dimethylamide function to a methyl-ester group by *O*-methylation with *Meerwein*'s and subsequent hydrolysis gave heptamethyl-5,15-dinorcobyrinate **25m**. This totally synthetic crystalline material was identified through direct comparison (HPLC, and UV/VIS, IR and ORD spectroscopy) with a sample of a corresponding 1,15-dinor-B_{12} derivative derived from vitamin B_{12} by methanolysis of a material obtained from *Karl Bernhauer*'s laboratory in Stuttgart [233][53]). *This was the first identification of a totally synthetic intermediate containing the B_{12} corrin chromophor by comparison with a compound derived by partial synthesis from vitamin B_{12}.*

This reassuring result in the undifferentiated natural series was achieved in an all-out effort by *Peter Schneider* in his thesis work [97] (*cf.* [17][208b][103]), based on the exploratory work of *Albert Fischli* [88] and *Hans-Ulrich Blaser* [95] in the model series (*cf. Fig. 12*); the achievement's prerequisite, of course, had been the regular supply of *A*/*D* component **25a** (R = COOMe) from Harvard to the ETH. To increase the product yield of the $A \rightarrow B$ cyclization step from an initial (spectroscopically estimated) 2% up to an eventual 72% for an overall process **25d** → **25l** (R = COOMe), consisting of not less than five delicate operations, took *Peter Schneider* about a year of intense work. The key observation that ended a long period of unsuccessful attempts to accomplish an $A \rightarrow B$ ring closure at both Harvard and the ETH was the formation of the c-*N*,*N*-dimethylamide function, accompanied by the exposure of the methylidene C=C bond by the treatment of the thiolactam/thiolactone **25d** with Me_2NH. In fact, such a treatment of a ring-*A* thiolactone turned out to be the solution not only for the $A \rightarrow B$ cyclization *via* sulfide contraction, but also for the $A \rightarrow B$ ring closure eventually achieved at Harvard *via* imido thioester/enamine condensation **25d** → **25e** → **25l** (R = COOMe; see below). Furthermore, it was to become one of the central steps in the photochemical variant of the B_{12} synthesis (attaching the ring *A* precursor **25g** to the *D*-*C*-*B* intermediate **25h** to give the tetracycle **25i**).

The replacement of Zn^{II} by Co^{III} in a corrinoid ligand – in the model series an exchange without any problems, consisting in acidolytic decomplexation, followed by treatment with Co^{II}-perchlorate and air oxidation in the presence of cyanide [9] – would, in the natural series, have presented a major preparative hurdle at various

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53) The totally synthetic material was later shown (after HPLC had become available) to consist of two diastereoisomers that differed in the configuration of the propanoic side chain in position e of ring *C*. This was also the case for the corresponding partially synthetic material derived from vitamin B_{12}. The latter was prepared by methanolysis of a sample of a 'B_{12}-oxidation product' obtained from *Bernhauer*'s laboratory. There, the surprising observation had been made [233] that treatment of the vitamin with $KMnO_4$ under special conditions oxidized the two *meso*-Me groups of the vitamin to carboxy groups, affording, after decarboxylation, the corresponding 5,15-dinor-B_{12} derivatives.

stages, had not the Harvard group made the important observation that Co^{II}-chloride is superior to Co^{II}-perchlorate as a reagent for introducing Co into *A*/*D*-secocorrinoid ligand systems. The reason for this difference in behavior between 15-CN-substituted ligand systems in the model series and the ligand in the natural series had to be seen in the higher sensitivity to oxidation of a chromophore system that is lacking the (electrophilic) CN substituent in the *meso*-position C(15).

Schneider's results came just in time for the Riga lecture, where they were prominently presented. The author did not attend the lecture, but reading its printed version [208b] led him to consider *Woodward*'s lecture in Riga as a model for how collaborative research should be documented and reported. The printed version of the lecture delineates and identifies the chemical essentials of each group's contributions to the progress of the collaborative work. This was the time when both the harmony and spirit of collaboration in the two groups were perhaps at their highest level. It was an important experience, since there had been a nagging doubt in the author's mind since the time he had read *Woodward*'s IUPAC London lecture of 1968 [208a] in print. From that progress report, there was no way of knowing whether any contribution at all had actually come from the ETH group.

What the printed version of the *Riga* lecture also shows is a telegram sent to *Woodward* from Cambridge to Riga, reporting on an improved yield in the $A \rightarrow B$ cyclization **25e** → **25l** (R = COOMe) by imido thioester/enamine condensation. This alternative $A \rightarrow B$ cyclization also started from the thiolactam/thiolactone **25d** (R = COOMe), involved the methylation of the thiolactam S-atom, the opening of the thiolactone ring with Me_2NH, and finally the ring closure by treatment with ^{t}BuOK. Harvard's success in accomplishing the cyclization by using (at room temperature!) that strong base nullified the earlier pessimistic prognosis of the author referred to above. Later, when the Harvard group succeeded in closing the corrin ring in the *differentiated* series (R = CN), and *Schneider*'s cyclization procedure became the one preferably used, *Woodward*, in his (printed) New Delhi lecture, referred to it – by what might appear to be a slight understatement – as being '*somewhat superior, in that it is relatively easier to reproduce, even though it is a very complicated sequence indeed*' [208c].

3.2.2. *Boston (July 26–30, 1971)*. After the *Riga* Conference, the Harvard group had to step back and to find a way of modifying the synthesis of the *A*/*D* component such that its *f*-propanoate group at ring *D* would be chemically differentiated from all the MeOCO groups of the *A*/*D* and *B*/*C* components. The task of modifying the *A*/*D* component turned out to be difficult, but was solved eventually with extraordinary chemical bravura. That splendid piece of research by which the problems in constructing **25a** (R = CN) were overcome (*cf.* pp. 153–157 in [208c]) may belong to the legendary collection of most brilliant research episodes in the oeuvre of *Woodward* and his collaborators in natural-product synthesis.

The *A*/*D* component **25a** (R = CN) with the ring-*D* propanoic acid function differentiated as CN group became available in spring 1971[54a]). Shortly before the

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[54]) a) Mentioned in the thesis of *W. Fuhrer* [102], p. 23; b) mentioned in the thesis of *P. Schneider* [97], p. 45; c) mentioned in the thesis of *H. Maag*, [103], p. 16; d) mentioned in the thesis of *W. Fuhrer* [102], p. 44.

Harvard group had this final *A*/*D* component in their hands, *Walter Fuhrer* at the ETH had in his hands already the first samples of a synthetic Co^{III}-corrin complex of the *differentiated* series, the pentamethyl-5,15-dinorcobyrinate-c-*N*,*N*-dimethylamide-f-carbonitrile **25l** (R = CN), synthesized by the photochemical *A*/*D*-secocorrin → corrin cycloisomerization[54b]). *Fuhrer* had started his thesis work in November 1969 [102], around the time when *Hans-Jakob Wild* [98] had shown in the model series that the *A*/*D*-secocorrin → corrin cycloisomerization is successful not only with a Pd^{II}-secocorrin complex, but also – actually more interestingly and more importantly so – within a chloro-Zn^{II}-secocorrin complex (*Fig. 23*), affording a corresponding corrin complex of which we knew already [9] that its metal ion can be replaced by Co. Starting from *B*/*C*-thiolactam-lactone **25b**, ring *D* precursor **25f**, and ring *A* precursor **25g**, *Walter Fuhrer* 'almost single-handedly'[54c]) accomplished, *via* **25h** and **25i** the synthesis of chloro-Zn^{II}-5,15-dinor-1,19-secocorrinate-*c*-*N*,*N*-dimethylamide-*f*-nitrile **25k** (M = ZnCl), observed its photochemical $A \rightarrow D$ corrin ring closure spectroscopically for the first time in January 9, 1971, had optimized the photochemical reaction step by end of May, and produced 'a few hundred milligrams' of hexamethyl-5,15-dinorcobyrinate-*c*-*N*,*N*-dimethylamide-*f*-nitrile **25l** (R = CN) as a mixture of diastereoisomers by June 1971[54d]).

To start from the *B*/*C* component **25b**, and develop a new strategy of corrin-chromophore construction and a final photochemical ($A \rightarrow D$)-ring closure to provide the central intermediate **25l** (R = CN) in the astonishingly short time of approximately one and half a year was only possible because of a multitude of most fortunate circumstances. Above all, there was that exceptionally brilliant trio of collaborators, *Walter Fuhrer* [102] and *Hans Maag* [103] as Ph.D. students, and *Peter Schneider* [97] as Ph.D. student and later as postdoc, whom to have in the laboratory was the author's great privilege, a trio supported by *Walter Schilling* as Ph.D. student [107], and by *Nayuroshi Obata*[55]) and *Naoto Hashimoto*[56]), and – in the final stages toward cobyric acid – *Andrew Holmes*[57]) as postdocs. Furthermore, there were a number of favorable *chemical* circumstances: *first*, the synthesis could start from the same *B*/*C* component already in use for the $A \rightarrow B$ variant[58]). *Second*, work towards a potential ring-*D* precursor, using as starting material the *enantiomer* of the starting material for ring *B*, had been launched already in 1967 in *René Wiederkehr*'*s* thesis work [91] and eventually directed towards compound **25f** [107], prone in 1970 to be attached to the *B*/*C* component *via* 'sulfide contraction *via* alkylative coupling'. *Third*, the ring *A* precursor **25g** that had to be attached to the tricyclic *B*/*C*/*D* intermediate **25h** did not differ from the precursor of ring *B*, **16a** (*Fig. 16*), but by the protection of the

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[55]) *Naruyoshi Obata*, postdoctorate ETH, 3.5.1971 – 30.11.1972

[56]) *Naoto Hashimoto*, postdoctorate ETH, 3.11.1969 – 24.4.1971

[57]) *Andrew Holmes*, postdoctorate ETH, 1.10.1971 – 5.10.1972

[58]) After the 'pre-Boston rush', *Walter Fuhrer* initiated and realized a modification of the sequence and number of steps in this synthesis, by showing that the construction of the secocorrin derivative **25i** is even shorter and more efficient by using, as starting material, the ring-*B* thiolactone/ring *C* thiolactam analog of the lactone/thiolactam **25b**, accessible directly from the ring *B* lactone/ring *C* lactam by treatment with P_2S_5. This is the version reported in the overall scheme of the photochemical variant of the B_{12} synthesis published in 1977 [29] in an article that also included the reaction conditions of all steps of the photochemical variant (see also concluding remarks below).

methylidene functionality. *Fourth*, the solution to the demanding problem of setting free the methylidene C=C bond at ring *B* of the tricyclic intermediate **25h** by treatment with Me_2NH could be taken over from *Schneiders*'s work on the $A \rightarrow B$ cyclization by sulfide contraction (**25d** → **25l**; R = COOMe). And *fifth*, the 'pacemaker' corrin synthesis in the model series (*cf. Sect. 2.7.* and *Fig. 24*), a project that had been initiated in parallel to the project in the natural series, did indeed what it had been intended to do, namely, 'paving the way' for the construction of the *A*/*D*-secocorrin chromophore along the path of the new strategy through providing UV/VIS data of constitutionally secured intermediates.

All theses favorable circumstances notwithstanding, coupling of ring *D* **25f** with the *B*/*C* component **25b** by 'sulfide contraction *via* alkylative coupling', converting the tricyclic coupling product **25h** to its thiolactone derivative by treatment with P_2S_5[58]), setting free the methylidene group at ring *B* of the tricyclic system by treatment with Me_2NH, joining the methylidene C-atom with the ring *A* precursor **25g** *via* iodinative coupling, achieving the contraction within the chloro-Zn complex to give the tetracylic complex **25i**, and, finally, deprotecting the methylidene group at ring *A* with a strong base, therewith setting the stage for the photochemical ring closure **25k** → **25l** (R = CN, M = ZnCl): all these steps carried out within one and half year under the pressure of the oppressive uncertainty, whether the final $A \rightarrow D$ cycloisomerization in this series might take place at all, and, if it would, whether it would choose the expected configuration of the critical *A*/*D* junction, were the *Herculean* achievement of that small group of outstanding Ph.D. students mentioned above [19]. The effort was richly rewarded by the final success of the photochemical cycloisomerization step. *Zinc* complex **25k** (M = ZnCl), when irradiated simply by visible light in strict absence of oxygen, cyclized to the corrin complex **25l** (M = ZnCl) with high efficiency and – when carried out at slightly enhanced temperature – with an *A*/*D* diastereoselectivity of *ca.* 2:1 in favor of the natural coil configuration, as determined after converting the Zn^{II}- to the dicyano-Co^{III} complex. When, soon *after* the Boston Congress, the cycloisomerization was performed with the Cd^{II} complex **25k** (M = CdCl), it proceeded in essentially quantitative yield and with an *A*/*D* diastereoselectivity of at least 20:1 in favor of the natural coil configuration of **25l** [102].

What, beyond all these fortunate circumstances mentioned above, turned out to be the most fortunate and perhaps also most important of all was the legendary HPLC column of *Jakob Schreiber*[59]), revered permanent member of the author's research group. That equipment [235], built by '*Schaggi*' by his own initiative and his own hands well in advance of the time in order to have the tool ready in the B_{12} struggle, became operating early 1971, just in time when *Walter Fuhrer* conducted his first successful photochemical experiments. What the '*Schreiber* column' [235] was able to separate

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[59]) *Jakob Schreiber* (1921 – 1992), the author's first Ph.D. student (1951 – 53) and subsequent permanent member of the group as '*Oberassistent*' until his retirement in 1986. Brilliant experimentalist and innovator of chemical equipments, instructor of Ph.D. students in experimental techniques, by his own initiative in charge for maintaining the group's competence in separation techniques. For a (chemical) biography, see [234]. At the time *Schreiber* built his HPLC equipment [235], he had close contact with Prof. *J. F. K. Huber* (Amsterdam) who had introduced HPLC into analytical chemistry [236].

were the otherwise inseparable diastereoisomeric dicyano-Co^{III}-5,15-dinor complexes obtained after the photochemical $A \rightarrow D$ cycloisomerization, the isomerism referring to the central *A*/*D* junction, as well as to the configurationally labile side-chain attachments at the corrin rings *A*, *B*, and *C*. The HPLC system became absolutely indispensable for spectroscopic characterization of the products formed in the synthesis' final phase, when, in almost each step, the Co^{III}-corrin complex formed would be a mixture of (peripheral) diastereoisomers. There was a time when *Woodward* sent one of his B_{12} postdocs (*Wolfgang Trommer*) over the Atlantic to the ETH (July 5./6.–10, 1971) in order to have him separate on the '*Schreiber* column' what (in the author's retrospection) must have been a mixture of 5,15-dinorcobyrinate derivatives, either before or after *C*-methylation. At Harvard, another postdoc, *Helmut Hamberger*, is said to have called upon a Massachusetts-based US company for help. Not only was the company delighted to oblige by bringing their most advanced LC system to the Harvard lab, but also seized the opportunity by sending out in a mail campaign to chemists throughout the US an advertisement showing an LC chromatogram of a synthetic B_{12} intermediate [237]. In his lecture at the IUPAC Conference in Boston (see below), *Woodward* gave an enthusiastic accolade to *Schreiber*'s column and the importance of *Schreiber*'s contribution in the critical end phase of the vitamin B_{12} project[50]). The '*Schreiber* column' [235] was arguably the first HPLC column used in organic chemistry for separating product mixtures in a natural-product synthesis.

In spring 1971, when at Harvard the *A*/*D* component **25a** (R = CN) finally had become available, the group was now quickly moving ahead by joining the *A*/*D* and the *B*/*C* components, and closing the corrin ring between rings *A* and *B* by *Schneider*'s procedure, as well as *via* the imido thioester condensation to produce pentamethyl-5,15-dinorcobyrinate-*N*,*N*-dimethylamide-*f*-nitrile **25l** (R = CN). The product formed by this alternative method of $A \rightarrow B$ cyclization also was obtained as mixture of peripheral diastereoisomers, yet in different proportions than obtained at the ETH *via* the photochemical $A \rightarrow D$ cycloisomerization. In both laboratories, these mixtures of diastereoisomers of **25l** (R = CN) eventually were separated by HPLC (by partition LC at the ETH and by absorption LC at Harvard), and the isomers, such as the one with the natural 3α,8α,13α-configuration at the propanoic-acid chain positions *b*, *d* and *e*, were isolated and spectroscopically characterized in pure form. *It was at this point that the two variants of the B_{12} synthesis came together again.*

From then on, the two groups were working in close parallel, eager to cross the finish line jointly before the IUPAC congress in Boston. *Woodward* and the author were scheduled to present lectures, the planning had it that *Woodward* would give a presentation of the $A \rightarrow B$ approach, and the author would disclose the photochemical variant of the B_{12} synthesis. The major remaining problem still to be solved in order to achieve these goals had been to introduce the two missing Me groups in the *meso*-positions C(5) and C(15) of the corrin chromophor. While at that time at the ETH *Peter Schneider* – by now as a postdoc – still had material to work with that he had produced in the undifferentiated, as well as in the differentiated, series by his $A \rightarrow B$ cyclization procedure, all the new material of the central intermediate **25l** (R = CN) produced at the ETH had now its origin in *Fuhrer*'s $A \rightarrow D$ cycloisomerization. Starting with *Winnacker*'s methylation procedure [90], developed in the model series (*cf. Fig. 14*),

Hans Maag and *Naoto Hashimoto* found the procedure to fail in inducing substitution at the single free *meso*-position between rings *B* and *C* of 'cobester' **1d** as a model substrate. However, when they replaced the reagent chloromethyl phenyl sulfide (*cf. Fig. 14*) with chloromethyl phenyl ether (working in the absence of Ag^+ ions in sulfolane as the solvent, followed by treatment of the reaction mixture first with PhSH and then with *Raney*-Ni), they obtained '10-methylcobester' in good yield [103]. Even more encouraging was the outcome of another exploratory experiment in which *partially* synthetic '5,15-bisnorcobester-($c \rightarrow 8$)-lactone' (available as a by-product in the methanolysis of *Bernhauer*'s B_{12} oxidation products; *cf.* above [233] (*cf.* [103])) was subjected to the same treatment: substitution at both C(5) and C(15) could be demonstrated to occur by isolating, as one of the products, 'cobester' **1d**. When *Peter Schneider* (working with material from $A \rightarrow B$ cyclization experiments) showed how the *N*,*N*-dimethylamide group at ring *B* of **25l** (R = CN) can be *oxidatively* cleaved by iodination (occurring at C(8)), proceeding with concomitant formation of the $c \rightarrow 8$ lactone group, the stage was set for studying the bis-methylation problem with the substrate **25n** in which the chromophore position between rings *B* and *C* would be sterically shielded against electrophilic substitution (*cf.* p. 90 in [107]).

Never had the Harvard/ETH collaboration been closer, yet also nervier, than in this critical and hectic 'pre-Boston' period, when any new information gathered in either group became exchanged by phone 'quasi instantaneously', a course of action that eventually discharged into the drama of 'black Friday' (July 9, 1971), just about two weeks before the IUPAC congress. In this debacle, both groups, in an investment of all their substrate material (at ETH: 60 mg of lactone-nitrile **25n**) into a concerted 'last-minute-methylation experiment' lost it all by unintentionally converting the differentiating CN group in the f-position into a MeOCO group (**25n** → **1d**). It happened because the reaction was run in chloromethyl methyl ether as the solvent (instead of as reagent), *i.e.*, a change in conditions which an exploratory experiment at the ETH had indicated to double the yield of bis-methylation product. As soon as the 'disaster' was recognized by taking the IR spectrum, the Harvard group was warned by phone, but it was already too late: the corresponding all-in-one-go experiment at Harvard had been started early that day and was irreversibly under way. The information so carefully 'stored' in the CN group over so many steps was lost. The damage caused by the loss of material was one from which to recover would require months.

At the ETH, however, *Peter Schneider*, *Walter Fuhrer*, and *Hans Maag*, after recovering from the debacle, embarked by their own initiative on a heroic 'day-and-night-shift operation', scraped together all the residual material from past $A \rightarrow D$ and $A \rightarrow B$ cyclization experiments and produced another 15 mg (as mixture of diastereoisomers) of 5,15-dinor-lactone-nitrile **25n**, which they ran through a low-yield but 'non-destructive' variant of the methylation procedure, and produced – all within essentially one week – *ca.* 120 μg of what (according to UV/VIS and HPLC) had to be the *f*-nitrile **25o.** After treatment with conc. H_2SO_4, followed by HPLC separation on the *Schreiber* column, they isolated two fractions of *ca.* 30 μg each, one of them assumed to be the 3α,8α,13α-hexamethylcobyrinate-*f*-amide **25p** and the other its 3α,8α,13β-diastereoisomer, both assignments based on the fact that their UV/VIS spectrum and their HPLC behavior could not be distinguished from those of the

corresponding samples derived from vitamin B_{12} [103]. The documentation of these results became the last few slides of *Woodward*'s, as well as the author's lecture, at the Boston event [19][60]). What at the time could only be assumed became a certainty shortly thereafter (see below): what the three undiscouraged young men had in their hands were indeed the first traces of totally synthetic hexamethyl-cobyrinate-*f*-amide **25p**[61]).

3.2.3. *New Delhi (February 6–12, 1972)*. The 'IUPAC Natural Products Meeting' in New Delhi was scheduled to take place within half a year after the Boston IUPAC International Congress. Both *Woodward* and the author were asked to present lectures; only *Woodward* accepted, and it turned out that he was right in doing so. What he announced in his New Delhi lecture under the title '*The Total Synthesis of Vitamin B_{12}*' [208c][62]) (see also [20]) was a *formal* synthesis of vitamin B_{12}, composed of complementary contributions from three different laboratories. Not only the synthesis of the vitamin itself, but also that of cobyric acid, were relay syntheses. What had been accomplished at the time the lecture was given was the *total* synthesis of 3*α*,8*α*,13*α*-hexamethylcobyrinate-*f*-amide **25p** (= **1e**), *ca.* 160 μg of a spontaneously crystallizing sample that had been prepared at the ETH *via* the photochemical *A* → *D* route with the Cd^{II} complex and identified by HPLC, UV/VIS, and CD (and shortly after the lecture by ^{1}H-NMR) comparison with a sample of *partially* synthetic *α*,*α*,*α*- hexamethylcobyrinate-*f*-amide. The relay compound prepared from vitamin B_{12} had been made available much earlier by *Hans Maag* [103][20] as one of the monoamides formed by partial ammonolysis of 'cobester' **1d**, and separation of the reaction mixture by thick-

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60) These events are described in detail by *Hans Maag* in his thesis [103] (pp. 107–110); see also [19]. Who was ultimately responsible for the debacle of 'black Friday'? If anybody, then the author. Because he should have thought of the possibility (what he did not) that those 'high-yield conditions' might not necessarily be harmless for the 'survival' of the CN group. Therefore, he neglected to insist that his (brilliant) student *Hans Maag* should check by taking the IR spectrum after the very first of the (in total eight) alkylation/reduction experiments he cautiously conducted with the all together 60 mg of lactone-nitrile **25m** available at that time at the ETH from *Fuhrer*'s photochemical cyclization experiments. However, the relative intensity of that CN IR band happens to be so low that *Maag* may well have correctly foreseen that it might be hopeless trying to run such a control with fractions that are so small. At the end, when he discovered the missing CN band, he had all together 15 mg of product material, distributed in three HPLC product zones, each of them he characterized separately by first recording an ^{1}H-NMR spectrum, recovering the material, then a UV/VIS, a CD, and eventually an IR spectrum. Background and events of 'black Friday' were described by *Woodward*, as well as the author [19], in their lectures at the IUPAC Congress in Boston[50]).

61) What they actually had in their hands was a binary mixture of the totally synthetic *α*,*α*,*α*- and the *α*,*α*,*β*-diastereoisomers of **25p** (see Figs. 34–37 in [19]).

62) The printed version of *Woodward*'s New Delhi lecture appeared about a year after the lecture had been delivered. It is a *postscript* of the lecture, since it includes results that were obtained by the Harvard group *after* the lecture had been given, *e.g.*, the important improvement of the reductive workup after the alkylation experiments with Zn-amalgam and AcOH (spring 1972; *cf.* [103], p. 109), a method distinctly superior to *Raney*-Ni used at the ETH, and also the use of BF_3/AcOH for the hydration of the *f*-CN group which is superior to the treatment with conc. H_2SO_4, originally used at the ETH, since it does not lead to partial epimerization at C(13) in ring *C* (fall 1972; *cf.* [103], p. 21).

layer chromatography and by HPLC on the *Schreiber* column[63]). Furthermore, such *partially synthetic* hexamethylcobyrinate-*f*-amide had already been converted in both laboratories to the corresponding *f*-acid **25q**, each group using their own method (*cf.* [208c]). From there, the Harvard group had made *partially synthetic* cobyric acid and identified it by comparison with the cobyric acid from natural sources, just in time for *Woodward*'s New Delhi lecture. Since cobyric acid had been already converted to vitamin B_{12} a decade earlier in the laboratory of *Bernhauer* at Stuttgart [147] (*cf. Table 1*), the *total* synthesis of 3α,8α,13α-hexamethylcobyrinate-*f*-amide **25p**, together with the *partial* synthesis of cobyric acid starting from partially synthetic **25p** as relay compound, amounted to a *formal* total synthesis of vitamin B_{12}.

It was possible to achieve this feat in time for *Woodward*'s lecture only because, in the rush between the Boston and the New Delhi Congress, *Woodward* and the author had agreed upon coordinating the work in the two laboratories as follows: the ETH group should concentrate on the preparation and characterization of the 3α,8α,13α-diastereoisomer of *totally synthetic* hexamethylcobyrinate-*f*-amide **25p**, to be prepared by the photochemical variant, and identify it by comparison with relay material obtained from vitamin B_{12}, whereas the Harvard group should focus on the conversion of such relay material **25p** prepared from vitamin B_{12} to *partially synthetic* cobyric acid and identify it by comparison with *natural* cobyric acid. Both groups succeeded to fulfill their programs just in time. Without this division of labor mutually agreed upon, it would not have been possible to complete the (formal) synthesis of vitamin B_{12} in time for *Woodward*'s lecture at the New Delhi conference. The last data collected for the spectroscopic identification of totally synthetic with partially synthetic **25p** were transmitted by phone from Zurich to New Delhi the very day of the lecture. Why the ETH and not the Harvard group was assigned to carry out the first identification of totally synthetic intermediate with a relay substance derived from vitamin B_{12} had a simple reason: to recover from the 'black Friday' debacle was faster *via* the photochemical variant than *via* the $A \rightarrow B$ cyclization route.

After New Delhi, the ETH group proceeded by consolidating and extending their identification steps, and the Harvard group now also made totally synthetic hexamethyl-α,α,α-cobyrinate-*f*-amide **25p** from material prepared *via* the $A \rightarrow B$ cyclization variant and also identified it with the relay *f*-amide derived from vitamin B_{12}. Both at the ETH and at Harvard, the identification of totally synthetic *f*-amide **25p** comprised both the 3α,8α,13α-, as well as the 3α,8α,13β-diastereoisomers, both purified by HPLC and obtained in crystalline form. Both groups also carried out the comparison of their material obtained by synthesis with material derived from vitamin B_{12} at the stage of the corresponding *f*-nitrile **25n**, and this again with both diastereoisomers α,α,α- and α,α,β. Later in 1972, the Harvard group proceeded further and prepared cobyric acid from totally synthetic *f*-amide **25o**, made *via* the $A \rightarrow B$ cyclization variant [208d]. The ETH group contented itself with the characterization and identification of

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[63]) The partial ammonolysis of cobester under the conditions used by *Maag* [103] (p. 226) led to a mixture of three mono-amido hexamethyl esters (besides starting material and minor amounts of a oligoamides) which were separated by thick-layer chromatography and purified by HPLC. The final confirmation of the constitution of the crystalline isomer that was assigned to bear the amide group in the *f*-side chain was actually its identification with the totally synthetic material **25p**.

the totally synthetic hexamethyl-α,α,α- and -α,α,β-cobyrinate-*f*-amides (and nitriles) prepared by the photochemical variant [102][103]. The group also went through the steps to cobyric acid, but starting with *partially* synthetic *f*-amide [107]. Later, *Woodward* and *Mark Wuonola* [209a], complying with a 'puritan principle' of research in natural-product synthesis, produced totally synthetic vitamin B_{12}[64]) from totally synthetic cobyric acid, essentially along the path *Bernhauer* had paved in his partial synthesis.

3.3. *Concluding Remarks.* In view of the mutual entanglement of the work accomplished at Harvard and the ETH in the end phase of the collaboration and the above-mentioned agreement on the division of labor for the sake of boosting *Woodward*'s New Delhi lecture, it does not make sense to speak of a 'first' and of a 'second' synthesis when referring to the two variants of the synthesis of vitamin B_{12}. Also, the two syntheses are methodically and structurally intertwined to such a degree that it would be inadequate to consider the photochemical variant as an achievement that stands completely on its own. Too much of chemical experience, gathered by the two research groups while working together on the original $A \rightarrow B$ variant, went into the execution of the photochemical $A \rightarrow D$ variant. On the other hand, it seems also fair to state that, without the decade-long systematic model studies on the basic problems of corrin chromophor construction and the massive amount of information that came from there, neither the ETH nor the Harvard group would have been able to achieve what they did, concept and execution of the exquisitely classical and radically *Woodward*ian synthesis of the Harvard *A*/*D* component of course exempted.

The *A*/*D*-secocorrin → corrin cycloisomerization on which the photochemical variant of the vitamin B_{12} synthesis is based, happens to supersede altogether what at the outset of the B_{12} project had been considered to be the most-demanding among the challenges of a vitamin B_{12} synthesis, namely, the stereoselective construction of an *A*/*D* component with its direct junction between rings *A* and *D*. The situation does not dispense with an element of irony, because without the advent of *Woodward* and *Hoffmann*'s generalized concept of sigmatropic rearrangements within the framework of orbital-symmetry control of organic reactions, the concept of the *A*/*D*-secocorrin → corrin cycloisomerization might perhaps never have been subjected to experimental test. The irony holds irrespective of whether the chemical impulse that triggered the development leading to the *Woodward–Hoffman* rules came up in the context of *Woodward* and *Ranganathan*'s struggle with the original variant of the *A*/*D* component of the B_{12} project [184], or whether this *A*/*D* struggle just happened to coincide in time with *Woodward* entering – prompted by a discussion with *E. J. Corey* on May 4, 1964 [238][239] – the final phase of his longstanding fight for understanding the stereoselectivity puzzle posed by *Emmanuel Vogel*'s [240] provoking ring-opening and ring-closure reactions.

There is some significance in pointing to the fact that the *Woodward–Hoffmann* rules did not stand at the beginning, but rather at the end of the path that led to the realization of the *A*/*D*-secocorrin → corrin cycloisomerization process (*cf. Fig. 19*), a path that sprung – as already mentioned – out of the vision of a B_{12} synthesis in which

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64) D-Ribose for the nucleotide chain, (+)-camphor for ring *C*, and (−)-camphor for ring *D* were still from natural sources.

the hidden biosynthetic symmetry in the B_{12} molecule would reflect itself in a chemical construction of all four rings from one single starting material. Had the *Woodward–Hoffmann* rules as such been likely to not only initiate the experimental testing, but also to trigger the perception of the *A*/*D*-secocorrin → corrin cycloisomerization without the need for such preliminaries, it might well have been at Harvard where the photochemical variant of the B_{12} synthesis had emerged.

There is a further element of irony along the thread that connects *Woodward*'s synthesis of the *A*/*D* component with the emergence of the *Woodward–Hoffmann* rules, the *A*/*D*-secocorrin → corrin cycloisomerization and the photochemical variant of the B_{12} synthesis: in the 1980s, in investigations carried out at ETH towards a chemical etiology of the B_{12} structure, taken up in the wake of studies on a possible relationship between the *A*/*D*-secocorrin → corrin cycloisomerization and the critical ring-contraction step in B_{12} biosynthesis, the nucleotide chain that, in the B_{12} structure, forms the characteristic nucleotide loop was found to be capable of regioselectively attaching itself to *undifferentiated* (!) heptakis(cyanomethyl)-corrinate to give – after ammonolysis – vitamin B_{12} as the sole isolated product [210][131][70] (*Fig. 26*). This (again 'targeted') discovery revealed in retrospect an opportunity which to think of would have been impossible the decades before, namely: *in both variants of the* B_{12} *synthesis, it would have been neither necessary to differentiate the* f*-carboxy functionality at ring* D*, nor to take a path to vitamin* B_{12} via *the relay station cobyric acid in order to accomplish a chemical synthesis of vitamin* B_{12}.

It remains a sobering fact that the collaboration between the Harvard and ETH research groups on the synthesis of vitamin B_{12} did not find its natural conclusion in the form of a joint scientific publication. The very existence of the photochemical *A* → *D* variant of the B_{12} synthesis as such, the way its emergence was handled by the author, the chemical entanglement of this alternative pathway with the original *A* → *B* variant, and not least the personal conditions that prevailed in the later 1970s for both *Woodward* and the author, are major reasons for this unfortunate outcome. What exists – besides (printed) Ph.D. theses from ETH and (unpublished) postdoctoral reports from Harvard and ETH – are published lectures [13][19][208a,b] and printed postscripts of lectures [17][24][29][208c][62]). The three representative *Woodward* lectures of which printed versions exist [208a,b,c] describe the original *A* → *B* variant of the B_{12} synthesis, most prominently including a synthesis within a synthesis, the *Woodward* synthesis of the *A*/*D* component. The New Delhi Lecture of February 1972, in which the '*Total Synthesis of Vitamin* B_{12}' was announced, dealt with the final phase of the joint project and was touching only very marginally upon the existence of the photochemical pathway. In *Woodward*'s concluding lecture on the completion and documentation of the (at that time still formal) total synthesis of vitamin B_{12} at the *Peter A. Leermaker* Symposium at the Wesleyan University (November 29, 1972), there was no mention of the existence of a photochemical variant of the B_{12} synthesis. This – in a way – was understandable to the author then – as it is now.

The photochemical variant of the B_{12} synthesis (with the cycloisomerization step on the Zn complex) had been presented for the first time in the author's lecture at the 1971 Boston Congress, describing the events up to two weeks after 'black Friday'. The manuscript for the printed account was submitted within a week after the lecture had been given and appeared in a (rather inaccessible) supplement volume of *Pure and*

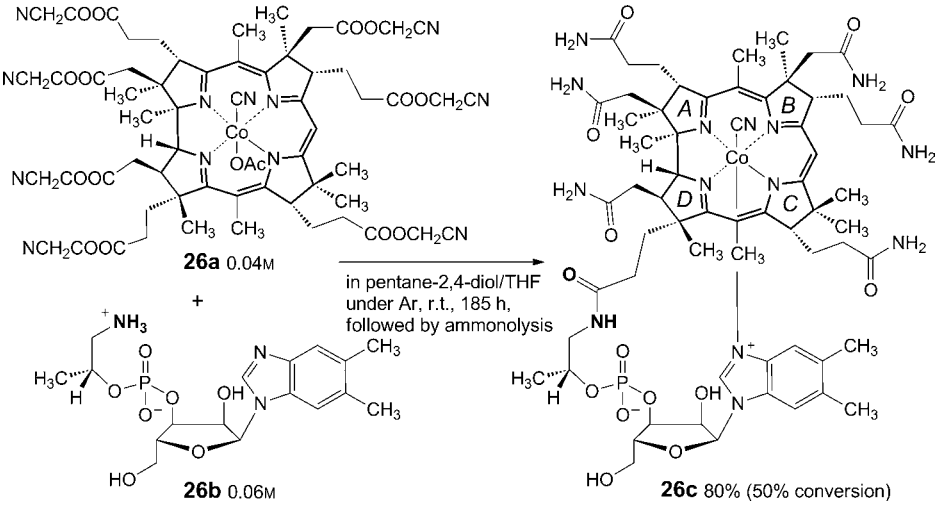

Fig. 26. *A conceptual and experimental amendment to the total synthesis of vitamin B_{12}.* About a decade after the B_{12} project had been completed, heptakis(*cyanomethyl*)-cobyrinate **26a**, under carefully controlled conditions, was found to react with the free nucleotide component **26b** *regioselectively* at the propanoate function in the f-position at ring *D*. The process (after ammonolysis) would have provided a synthetic access to vitamin B_{12} without the need of a prior differentiation of the ester group in the f-position from all other ester groups and of using cobyric acid as a relay compound [70][131][210].

Applied Chemistry [19][50]). The final version with the photochemical step carried out on the *A*/*D*-secocorrin-Cd^{II} complex was accomplished in the period between Boston and New Delhi Meetings, but remained unpublished until a postscript based on the author's lecture given at the *Zurich Chemical Society* appeared in print in 1974 [24]. An English translation (by *Claude Wintner*) of this publication, complemented with the formula scheme of the photochemical variant, eventually appeared in 1977 [29][65]). This latter publication was meant as a way out of what the author increasingly felt to be a dilemma. In view of the conceptual and methodological entanglement of the two variants of B_{12} synthesis, the author's conviction had been that a joint Harvard/ETH publication of the synthesis of vitamin B_{12} would have to encompass both variants, and that an independent separate publication of the photochemical variant would be inappropriate. The rather unusual title of the two publications of the author's lecture ('*Organische*

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[65]) The experimental procedures that constitute the photochemical variant of the B_{12} synthesis are accessible in printed theses of *Walter Fuhrer* [102], *Hans Maag* [103], and *Walter Schilling* [107], and the procedures of the reaction steps studied at ETH in the context of the joint Harvard/ETH project in the theses of *Jost Wild* [80], *Urs Locher* [81], *Alexander Wick* [82], *Peter Löliger* [87], *René Wiederkehr* [91], *Paul Dubs* [92], *Willi Huber* [93], *Lucius Werthemann* [89], and *Peter Schneider* [97]. Today, all these theses are available with their full text in the Internet '*ETH e-collection*' under the names of the respective authors.

Naturstoffsynthese heute – Vitamin B_{12} als Beispiel' [24] and '*Natural Product Synthesis and Vitamin B_{12}*' [29], respectively) reflect this dilemma. The author imposed on himself not to use the straight title 'Synthesis of Vitamin B_{12}' for this article because, at that time, he still believed that this was the title to be kept in reserve for the joint publication by the two research groups of what they had accomplished in the joint adventure they had gone through and had enjoyed so much.

4. The Photochemical *A*/*D*-Secocorrin → Corrin Cycloisomerization: Mechanism and Scope of the Reaction (1973–1978). – Even before the 'pacemaker' model synthesis had been launched, investigations in the heptamethyl-corrin model series were directed toward questions referring to the mechanism of the cycloisomerization process, first and foremost to the relationship between the nature of the coordinating metal ion and the occurrence or non-ocurrence of the photochemical ring-closure reaction. The quest was to explore properties and scope of the cycloisomerization process as a prerequisite of finding the optimal conditions for accomplishing the $A \rightarrow D$ ring closure in the natural series where the process was expected to be constitutionally, as well as stereochemically, far more demanding than in the model series. As described in *Chapt. 3*, that goal was reached by *Walter Fuhrer* [102] in his near-to-optimal final achievement of the light-induced cycloisomerization of a Cd^{II}-*A*/*D*-bisnor-secocobyrinate intermediate as the central step of the photochemical variant of the B_{12} synthesis. In the wake of *Hans Wild's* seminal accomplishments in the model series [17][28][98], *Niklaus Bühler* in his thesis [101] investigated the synthesis and photochemical cycloisomerization of *A*/*D*-secocorrinates deuterated at the CH_2(19) in ring *D* in order to establish the position of the D-atom after the 1,16-sigmatropic shift. His mechanistic investigations were then taken up by *Reinhart Neier* in his thesis [113], focusing on photo-mechanistic aspects of the process, such as wavelength dependence, luminescence, sensitization, and quenching. His results [28][113], together with those of *Bühler* [101] and additional observations made on the process in the laboratories of *Gerhard Quinkert* [241b] in Frankfurt and of *Andrew J. Thompson* [241a] in Norwich (GB), provided insights into the nature of the light-induced cycloisomerization process that were as relevant as they were surprising. *Sect. 4.1.* summarizes them in some detail.

4.1. *Studies Referring to the Mechanism of the* A/D-*Secocorrin → Corrin Cycloisomerization* [28][101][113]. For a 'targeted discovery' of what in organic synthesis may qualify as a new reaction, its 'mechanism' becomes an issue even before the occurrence of the reaction is established. As described at some length in *Sect. 2.6*, at the origin of the path to that 'discovery' was a playful juxtaposition of the formulae of two isomeric ligand systems and an equally playful recognition of structural transformations that formally might connect the two isomers. The decisive step was the conceptual identification of those formal transformations as special cases of what *Woodward* and *Hofmann* around that time had defined as generalized classes of reaction: $(1 \rightarrow n)$-sigmatropic H shifts and $\pi \rightarrow \sigma$ electrocyclizations. Originally, steric considerations had called for coordination of the tetradentate secocorrin ligand by a metal ion as a prerequisite of such a ring closure to occur, and the first exploring experiments were undertaken in complete ignorance of other influences the coordinating metal ion might exert on the photochemical process. The lesson those experiments then taught us was

twofold: the original idea according to which the reaction would demand a robust 'square-planoid' coordination to bring reactions centers into close proximity is in essence irrelevant; of decisive importance for the occurrence or non-occurrence of the reaction are the electronic structure and the physical properties of the coordinating metal ion after photoexcitation (*cf. Fig. 23*).

An early initiative towards exploring the mechanism of the *A*/*D*-secocorrin → corrin cycloisomerzation was tracing the path of the sigmatropic shift of the H-atom by demonstrating it to actually end up as one of the H-atoms of the Me(20) group at C(1) of the corrin complex. Metal complexes of the 19,19-dideuterosecocorrin ligand **27f** (M = H; *Fig. 27*) were synthesized by the reaction sequence familiar from *Fig. 21*, using the ring-*D* precursor **27e**, prepared from mono-thio-succinimide by the sequence **27a** → **27b** → **27c** → **27d** → **27e**. The cyclization of the Pd^{II} complex **27g** of the 19,19-dideuterosecocorrin by irradiation with visible light in CH_2Cl_2 to a Pd^{II}-dideutero-corrinate **27k** (isolated in 72% yield) took 36 h for completion, as compared to 4 h for the cyclization of the corresonding Pd^{II}-19,19-*dihydrogen*secocorrinate under the same conditions. The ^{1}H-NMR spectrum of the cyclized complex in the dideutero series no longer showed the *multiplet* (4.6 – 4.9 ppm) of H–C(19) in the spectrum of the non-deuterated analog, and the Me signal at the highest field (1.25 ppm, $CDCl_3$, 100 MHz) no longer was a sharp *singlet*. A kinetic analysis of the cyclization **27g** → **27k** carried out in EtOH at 32° (first-order in **27g**, monitored wavelength 500 nm) revealed a primary isotope effect of 7.0 (±0.7). For the cyclization of the Zn^{II}-19,19-dideuterosecocorrin complex **27i** to **27l**, the corresponding value was 3.8 (±1.0)[66]. *These findings confirmed the constitutional course of the sigmatropic (1 → 16) H shift and indicated this migration to be the rate-limiting step of the cycloisomerization process.*

Syldatk and *Quinkert* [241b] in Frankfurt determined the quantum yield of the cyclization of the Pd^{II}-*A*/*D*-secocorrin complex **21g** (M = Pd) in $CHCl_3$ to be exceedingly low (0.008 at 20°; approaching zero at low temperatures). They also showed that, in contrast to the corresponding corrin complexes, neither the Pd^{II}- nor the chloro-Zn^{II}-*A*/*D*-secocorrin complex show luminescence. *Gardiner* and *Thomson* [241a] at the University of East Anglia carried out a comprehensive study on the luminescence properties of the whole series of synthetic *corrin* complexes. Their results revealed a striking parallelism between those closed-ring metal corrinates which display corrin luminescence, and the secocorrinates that undergo facile photocyclization and provided data which led them to conclude '*that the presence of low-lying metal d-states quenches both the emission of the corrin chromophore and the photochemical ring closure of the secocorrin*' [241a]. Their interpretation of the striking difference between the behavior of the first-row transition metal ions such as Ni^{II} and the higher-row transition metal ions such as Pd was the postulate that the metal ion's d-state in the case of the first-row metal ions is energetically below, and in higher-row metal ions above the lowest triplet state of the corrinate chromophore.

At the ETH, the photochemical studies pursued by *Niklaus Bühler* [101] and *Reinhard Neier* [103] showed the cylization of the Pd complex **21g** (M = Pd) to follow

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[66]) For a detailed report on these measurements see [101] (p. 55 – 86). For primary kinetic isotope effects between 5 and 12 of thermally induced sigmatropic 1,5-H shifts see [242] and of light-induced triplet-H transfers, see [243].

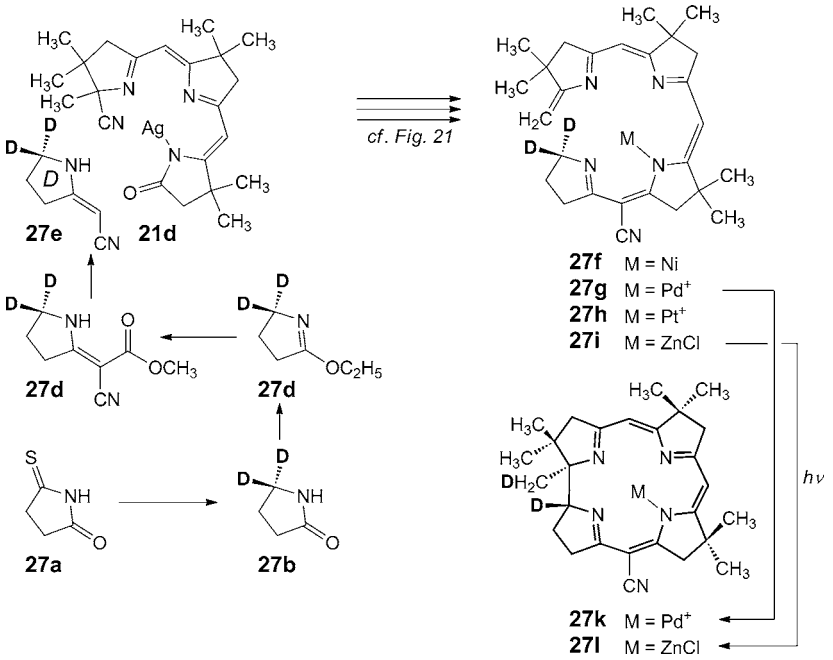

Fig. 27. *^{1}H-NMR-Spectroscopic demonstration of the (1 → 16) H shift from C(19) to C(20) in the cycloisomerization reaction of 19,19-dideutero-*A/D*-secocorrinates* **27g** *and* **27i** [101].

Reaction conditions [101]: **27a** → **27b**: $NaOD_2$/Ni-Al/D_2, D_2O/dioxane, r.t.; 55/74% yield; 88% dideuterated, ±5%; **27b** → **27c**: $Et_3O^+ \cdot BF_4^-$, CH_2Cl_2, reflux; 73%; **27c** → **27d**: methyl 2-cyanoacetate, 100°; 73%; **27d** → **27e**: 1N NaOH, 100° → conc. HCl, r.t.; 95% yield; 89% dideuterated, ±2%; **27e** + **21d** → **27f**,**g**,**h**,**i** : see *Figs. 21* and *23*; **27k** → **27k**: *hν*/visible, 150-W lamp, CH_2Cl_2, 40°; 72%.

essentially first-order kinetics, being only very weakly influenced by the presence of oxygen, whereas the cyclizations of the corresponding complexes of Zn and Cd, apart from being very efficiently quenched by oxygen, displayed far more complex kinetics. Sigmaoid plots of product formation *vs.* reaction time clearly demonstrated *the* A/D-*secocorrin → corrin cycloisomerizations of the Zn^{II}- and the Cd^{II}-secocorrin complexes* **23a** *(*M = Zn-Cl/Cd-Cl) *to be product-sensitized photoreactions* (*Fig. 28* and *29*). This was further supported by 'action spectra' which showed that product formation rates observed at specific irradiation wavelengths plotted against wavelength clearly followed the pattern of the UV/VIS-absorption spectra of the *corrin* complexes and not that of the corresponding *s*ecocorrin complexes (*Fig. 29*). The extreme sensitivity to oxygen of the Zn and Cd complex pointed to a process proceeding *via* an electronically excited *triplet state*, *a* conclusion corroborated by the observation that the reaction is efficiently quenched by the *Ullmann*'s triplet-state quencher [103][244], as well as by the finding that the reaction can be sensitized by typical triplet sensitizers such as bengal rosa or eosin [113].

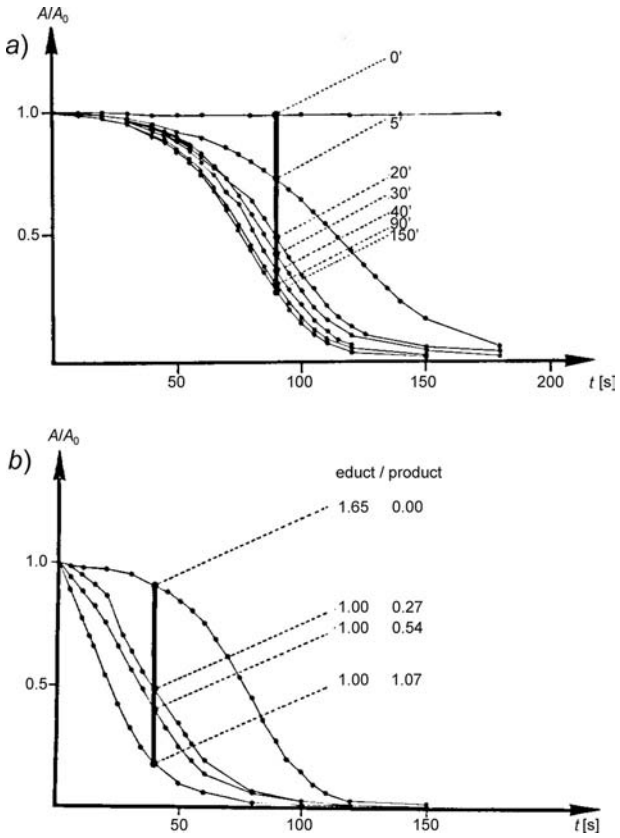

Fig. 28. *Sensitivity to atmospheric oxygen and sensitization by the cyclization product of the cycloisomerization* **23a** → **23b** (M = Zn–Cl; *c* of $4.1 \cdot 10^{-5}$ and $6.7 \cdot 10^{-5}$ mol/l; irradiation at 500 nm, in EtOH, 32°). *a*) Product formation *vs.* time plots as observed at varying times of degassing (0 → 150 min.) of the reaction medium with Ar [101] (p. 39). *b*) Product formation *vs.* time plots as observed in experiments with product added at the start of the reaction in different molar educt/product ratios (1.65 : 0.00 → 1.00 : 1.07) [101] (p. 40).

Fig. 30 points to a remarkable relationship between purely constitutional aspects of tetracyclic, as well as tricyclic, corrinoid chloro-Zn^{II}-complexes and the occurrence of fluorescence: the two complexes containing the methylidene C=C bond at ring *A* do not show fluorescence, while all the listed complexes in which that C=C bond is absent, do so [113]. The methylidene group appears to be responsible for the absence of fluorescence, and implicitly, for the photochemical *A* → *D* cycloisomerization to require a sensitizer in order to proceed. In fact, the cycloisomerization **23a** → **23b** (M = Zn–Cl) is not only sensitized by its product complex **23b**, but can also be sensitized with similar efficiency by the *A*/*D*-secocorrin complex **21f** (M = Zn–Cl), the

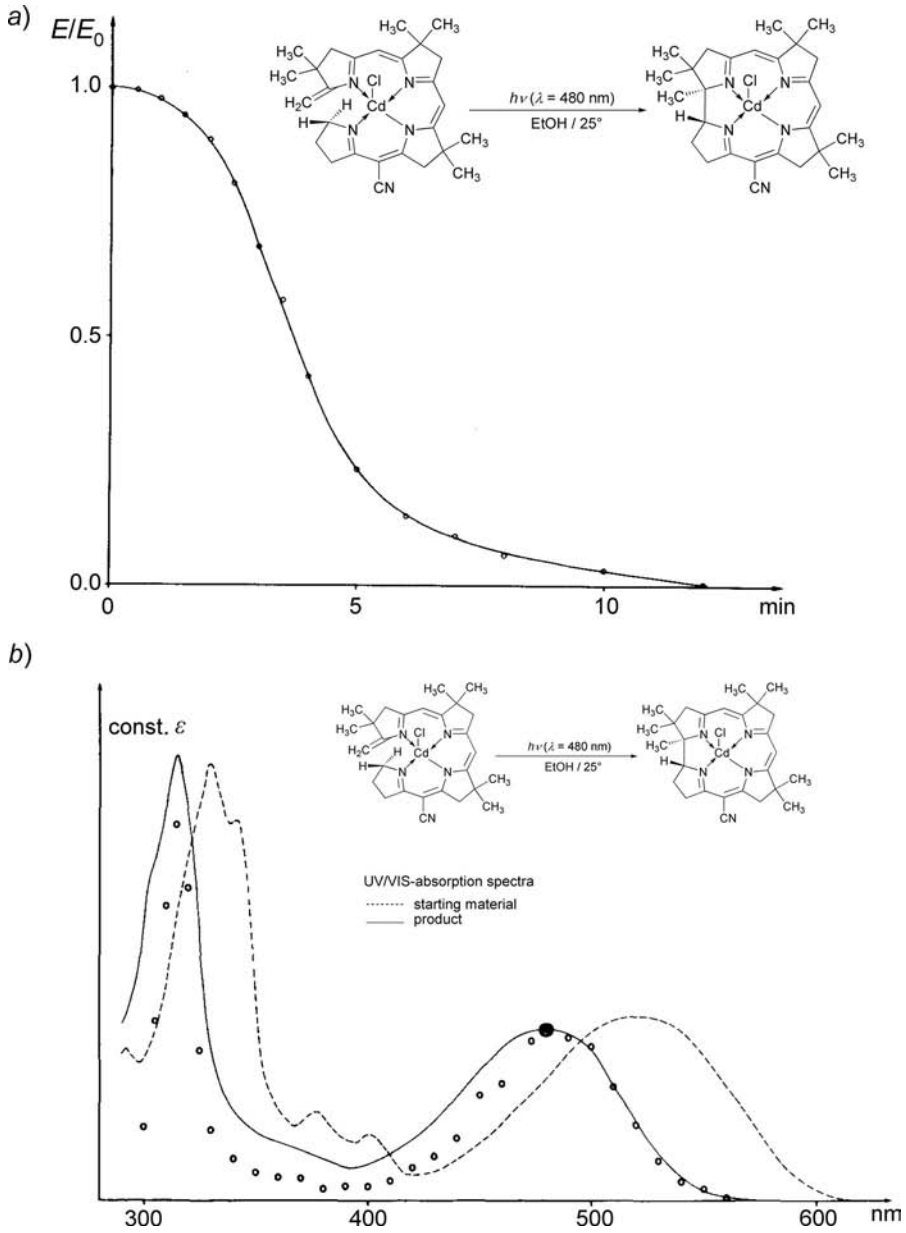

Fig. 29. *Cycloisomerization* **23a** → **23b** (M = Cd-Cl; *c* of $3.0 \cdot 10^{-5}$ and $3.23 \cdot 10^{-5}$ mol/l, irradiation at 480 nm, in EtOH, 25°). *a*) Monitoring product formation and reaction time by UV/VIS spectroscopy produces a curve that (qualitatively) is characteristic for a product-sensitized process [113] (p. 14). *b*) 'Action spectrum' at reaction mid-time by UV/VIS spectroscopy: the 'spectrum' (dots) parallels the UV/VIS spectrum of the corrinate product and *not* that of the *A*/*D*-secocorrinate educt [113] (p. 15 and Table 2, p. 47).

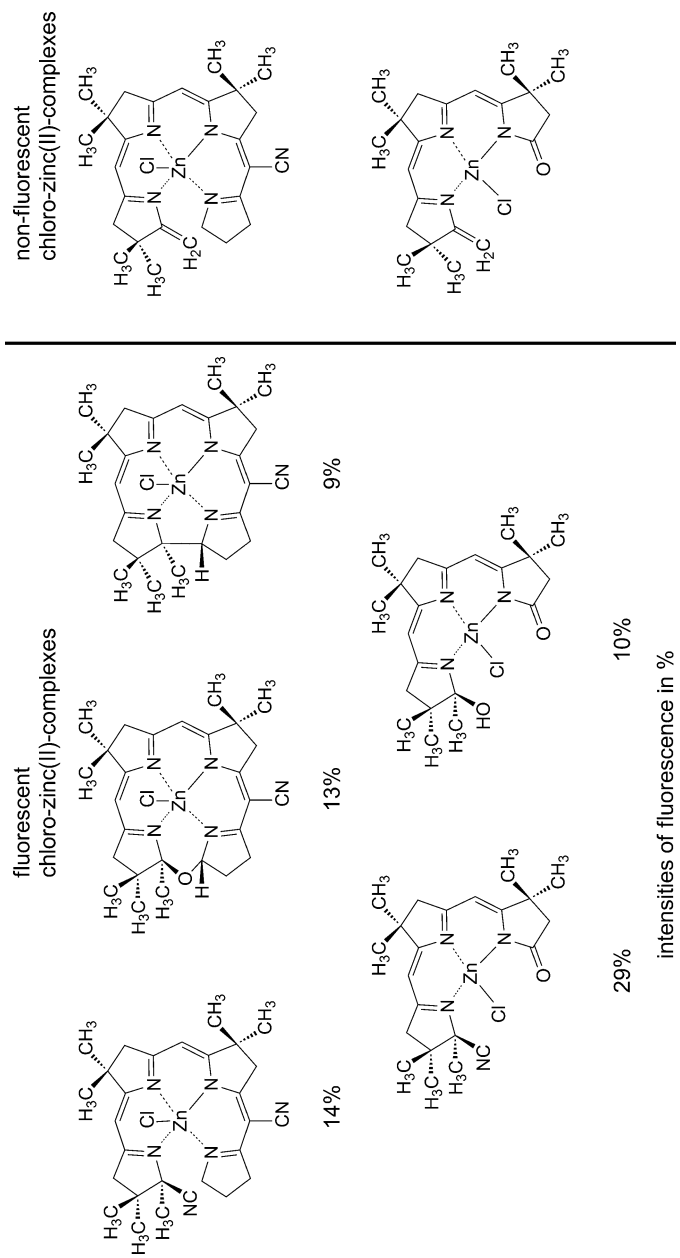

Fig. 30. *Fluorescence is observed in tetracyclic and tricyclic corrinoid chloro-Zn^{II} complexes that do not possess a free methylidene group at ring* A, *while corresponding complexes with unprotected methylidene group at ring* A *do not exhibit fluorescence* [113]. The methylidene group seems to provide a pathway for radiationless decay of the photoexcitation that is more rapid than intersystem-crossing, this being the reason for the cycloisomerization requiring sensitization in order to proceed.

ligand of which happens to be the precursor of the *A*/*D*-secocorrin ligand **23a** in its preparation[67]).

A necessarily qualitative and highly simplified view on what supposedly is going on in the photoactivation of a chloro-Zn^{II}- or chloro-Cd^{II}-*A*/*D*-secocorrin complex is outlined in *Fig. 31:* irradiation of the secocorrin complex produces a singlet excited state that deactivates itself by non-radiating decay too fast for a reaction to proceed and faster than it changes to a more stable triplet state. Irradiation of the corresponding corrin complex produces an excited singlet state which – in contrast to the one of the secocorrin complex – lives long enough in order to be able to populate a triplet state which, *via* sensitization, populates the lower-lying, long-living triplet state of the secocorrin complex. From the latter would take off the sigmatropic H shift, leading to the *A*/*D*-secocorrin diradical, which – after or concomitant with intersystem crossing – undergoes the $1 \rightarrow 19$ $\pi \rightarrow \sigma$ collapse.

Assuming an involvement of the methylidene C=C bond in a rapid radiationless decay of photoexcited singlet state of the *A*/*D*-secocorrinate, the question was raised as to whether the photoexcitation of the chromophore of such a secocorrin complex might imply a rotational movement around the methylidene C=C bond axes. A series of (delicate) experiments negated this question: samples of chloro-Cd^{II}-*A*/*D*-secocorrinate **32b** (M = Cd–Cl) *mono*deuterated at the methylidene C-atom with non-equilibrium *endo*/*exo*-ratios were recovered diastereoisomerically unchanged after irradiation with visible light in non-degassed $CDCl_3$ solution [113] (*Fig. 31*). Whatever pathway the methylidene group at ring *A* might offer to a non-radiative decay of the excited singlet state, it does not seem to imply a configurationally equilibrating rotation around its bond axis.

The preparation of these monodeuterated substrates proceeded *via* the two diastereoisomeric mono(iodo)methylidene derivatives **32a**, obtained from the Ni^{II}-secocorrinate **21g** by iodination of the latter with NIS, subsequent reductive replacement of the I substituent by D, and finally replacement of the coordinating Ni ion by Cd^{II}. These transformations may appear to have been laboratory routine, but in reality they were experimentally extremely demanding, especially in avoiding con-

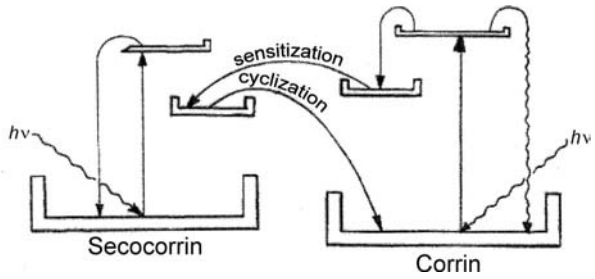

Fig. 31. *Qualitative overview of the photoexcitation path in the light-induced* A/D-*secocorrin → corrin cycloisomerization reaction* (for details, see the text).

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[67]) In preparative *A* → *D* cycloisomerization experiments **23a** → **23b**, it may well be that traces of **21f** as impurities present in **23a** act as sensitizer and thereby as reaction starter.

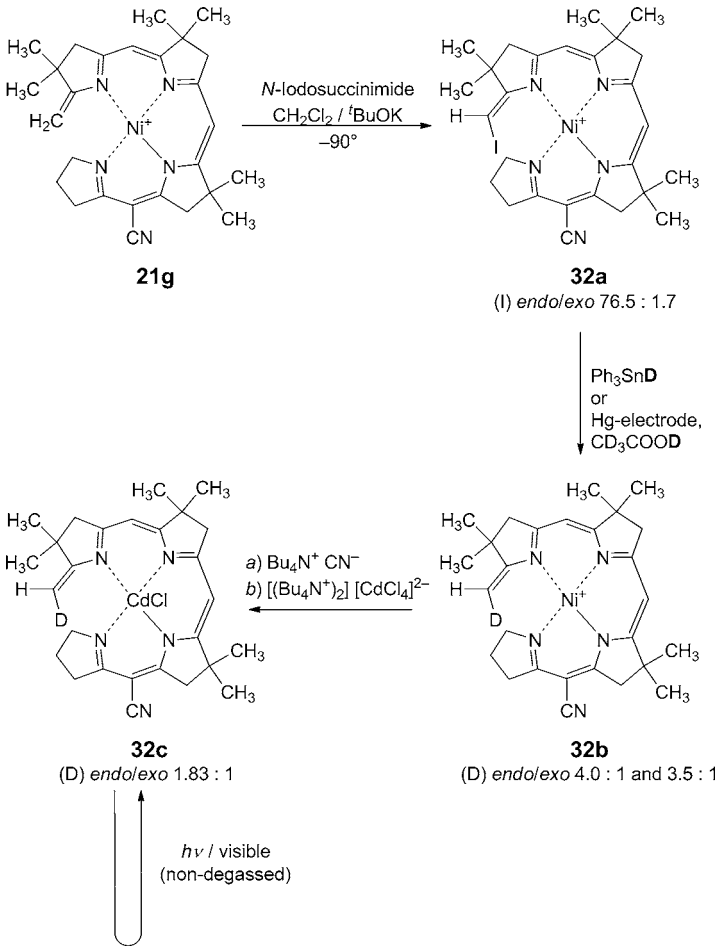

Fig. 32. *Irradiation of the monodeuterated chloro-Cd^{II}-secocorrinate* **32c** (in the presence of air, no cyclization) *does not seem to cause a change in the* exo/endo *ratio of deuteration at the methylidene C-atom*. Rotation around the C=C bond axes of the methylidene group does not seem to be part of the radiationless deactivation pathway [113].

Reaction conditions [113]: **21g** → **32a** (at r.t.): NIS, CH_2Cl_2/ ^{t}BuOH, r.t.; 95%; (I) *endo*/*exo ca.* 2 : 3; iodination at 10° → *endo*/*exo* 3 : 1; iodination at 80° in CH_2Cl_2 → *endo*/*exo ca.* 1 : 4; **21g** → **32a** (at − 90°): NIS, CH_2Cl_2, CF_3COOH (76% *endo*/1.7% *exo*); **32a** (*endo*/*exo ca.* 1 : 2) → **32b**: Ph_3SnD, azobis(isobutyronitrile), $CHCl_3$, *hν* visible (200-W; W lamp); 75%; (D) *endo*/*exo ca.* 4 : 1; **32a** (I) *endo* → **32b**: electrochemical reduction, Hg electrode, − 910 mV, $LiClO_4$, PhCN, CD_3COOD; 68%; (D) *endo*/*exo ca.* 3.5 : 1; **32b** ((D) *endo*/*exo ca.* 3.5 : 1) → **32c**: Bu_4NCN, → di-tetrabutylammonium $CdCl_4$, $CHCl_3$, in the dark; 87%; (D) *endo*/*exo ca.* 1.9 : 1. No discernable change in the ^{1}H-NMR spectrum of this product after irradiation with 200-W W lamp for 2 h (without degassing!).

figurational equilibration of the monodeuterated methylidene group in the step **32b** → **32c**. Full details of the investigation are described in *Reinhard Neier*'s thesis [113] (p. 89 – 121).

4.2. *Stereoretention in the Photochemical* A/D-*Secocorrin* → *Corrin Cycloisomerization of an (19*S*)-19-(Methoxycarbonyl)*-A/D-*secocorrinate* [28][101]. Besides his involvement in mechanistic problems (see above), *Niklaus Bühler* in his thesis [101] took up by his own initiative the synthesis of the chloro-Cd^{II}-(19*S*)-*19-(methoxycarbonyl)-A*/*D*-secocorrinate **33d**, a model system that contains a substituent (the MeOCO group) at the point of departure of the H-atom in the sigmatropic H shift (*Fig. 33*). The outcome of an *A* → *D* ring closure in such a chiral *A*/*D*-secocorrinate was expected to provide information about the stereochemical behavior of the reaction's elusive reaction intermediate.

The synthesis of (19*S*)-**33d** followed the pattern of previous model syntheses, starting with the already known tricyclic Ag^{I} complex **21d** (*cf. Fig. 21*), and proceeding – after coupling with the optically active ring *D* precursor (*S*)-**33a** by an imino ester/enamine condensation – *via* the Ni^{II}-*A*/*D*-secocorrinates (19*S*)-**33b** and (19*S*)-**33c** – to the target compound. The ring-*D* precursor was prepared by the procedure already known (*cf. Fig. 6* and *21*) from the preparation of other ring-*D* precursors: L-pyroglutamic acid was *O*-alkylated with *Meerwein* salt, the imido ester was condensed with *tert*-butyl 2-cyanoacetate, and the *tert*-butyl ester group of the adduct selectively cleaved and concomitantly decarboxylated. The deprotective elimination of the CN group (19*S*)-**33b** → (19*S*)-**33c**, as well as the *trans*-complexation (19*S*)-**33c** → (19*S*)-**33d** were reaction steps of major concern, both because of a possible deprotonation (and partial racemation) at C(19) under strongly basic reaction conditions. The first of these steps succeeded by treating (19S)-**33b** with ^{t}BuOK in ^{t}BuOH under carefully controlled conditions[68]). In the step (19*S*)-**33c** → (19*S*)-**33d**, strict maintainance of near neutrality in the reaction mixture was required in order to avoid racemization of the free ligand transiently present in the course of the reaction (*Fig. 34*). No problem, however, was encountered in the final step where an oxygen-free ethanolic solution of the chloro-Cd^{II}-secocorrinate (19*S*)-**33d** (a single species) was exposed to visible light: the *A* → *D* cycloisomerization proceeded smoothly to the corrin complex (19*S*)-**33e** isolated in crystalline form and high yield.

X-Ray structure analyses of the *A*/*D*-secocorrin complexes **23a** (M = Ni^{+}, Pd^{+}, Pt^{+}) of the standard model series [245][98] (*cf.* Fig. 19 in *Part VI* of the series) had confirmed the proximity of the reaction centers relevant to the *A* → *D* ring closures of such complexes. Still another such analysis became available for the chloro-Cd^{II} complex **34a** (= **23a**; M = Cd–Cl) [98][24][29] (*cf.* structure **34b**[69]) in *Fig. 34*). On the basis of this information it could be assumed that the coil configuration of the secocorrin complex (19*S*)-**33d** would be the one abstracted by formula **34c**[69]) in which

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[68]) The workup of the deprotection step (19*S*)-**33b** → (19*S*)-**33c** required a re-esterification with CH_2N_2, since the treatment with the strong base in highly diluted solution led to (partial) replacement of the MeOCO by COOH group, presumably due to traces of moisture. The deprotection failed, when (19*S*)-**33b** was, for instance, warmed in DBU as solvent, leading to a product mixture that contained a component most probably formed by an aberrant '*Dieckmann* cyclization' between the CN group at C(1) and C(19).

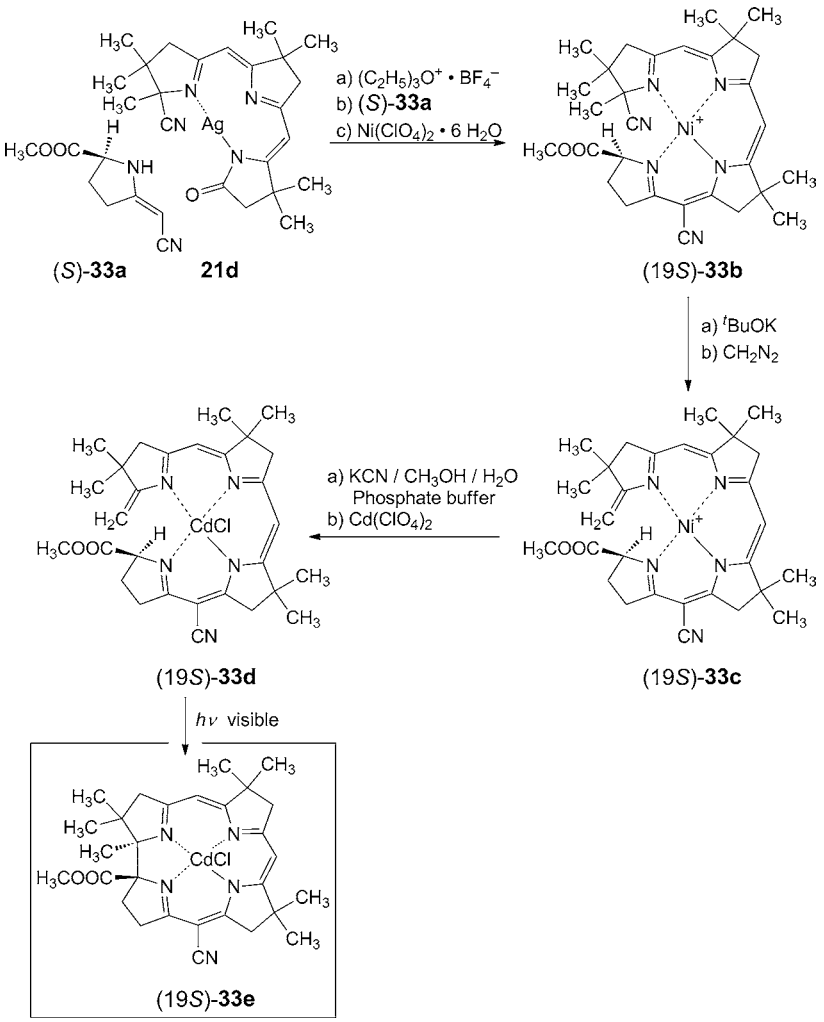

Fig. 33. *The light-induced cycloisomerization of the (19*S*)-chloro-Cd*^{II} *complex* **33d** *to* **33e** *proceeds* (predominantly, if not completely) *by retention of configuration at the reaction center C(19)* [101].

Reaction conditions [101]: **21d** + (*S*)-**33a** → (19*S*)-**33b**: a) Et_3O^+ BF_4^-, $EtN(^iPr)_2$, CH_2Cl_2, r.t.; *b*) (S)-**33a**, CH_2Cl_2, r.t., Ar, 20 d in the dark; c) $Ni(ClO_4)_2 \cdot 6\ H_2O$, $EtN(^iPr)_2$, MeCN, r.t.; 35%; (19*S*)-**33b** → (19*S*)-**33c**: a) ^{t}BuOK in ^{t}BuOH, 70°; b)CH_2N_2[68]), MeOH/Et_2O, r.t.; 53%; (19*S*)-**33c** → (19*S*)-**33d**: KCN, Na-Phosphate buffer, pH 6.8, MeOH, H_2O, $Cd(ClO_4)_2$/NaCl, Ar, r.t.; 61%; (19*S*)-**33d** → (19*S*)-**33e**: *hν* visible (200-W; W lamp), degassed (Ar), EtOH, r.t.; 82,5%.

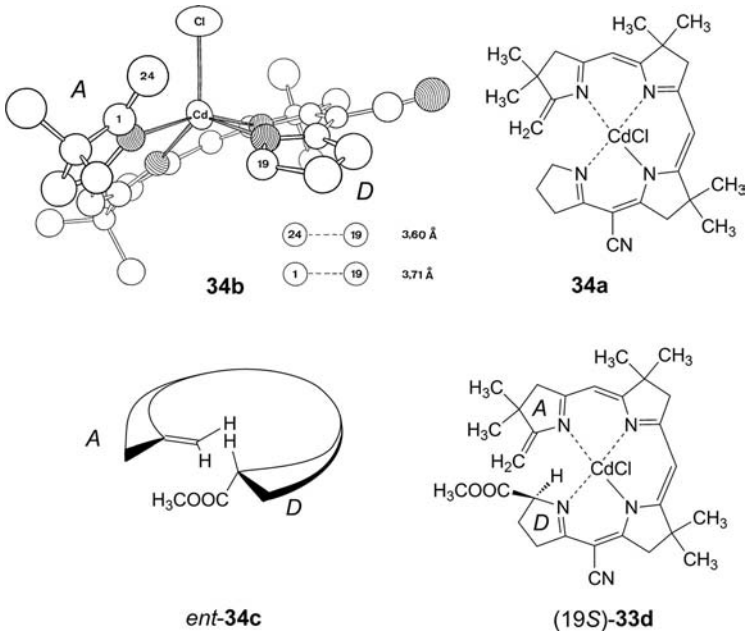

Fig. 34. *The X-ray structure*, **34b**, *of* (racemic) *chloro-Cd*^{II}-A/D-*secocorrin complex* **34a** (= **23a**; M = Cd-Cl) *corresponds to the coil presentation* **34c** *of the* enantiomer *of (19*S*)-***33d***[69]).

the H-atom at C(19) – and not the MeOCO group – is pointing towards the methylidene C=C bond at ring *A*. A comparison of the CD spectra of the Cd–Cl (19*S*)-**33d** before and after the photochemical cyclization clearly showed this coil configuration (at least partially) be maintained throughout the cycloisomerization. Given the possibility of a (partial) racemization in the preparation, as well as the cyclization process of (19*S*)**-33d**, no values can be given for the configurational purities of either the secocorrin or the corresponding corrin complex. However, a comparison of the CD spectrum of the corrinium cation derived from (19*S*)-**33e** (by acidification of its EtOH solution) with the CD spectrum of the corrinium cation derived from a totally synthetic chloro-Cd^{II}-corrinate in the natural series (*cf.* formula **25l** in *Fig. 25*[70])) pointed to a high degree of such purity (*cf. Part VI* of this series). To that (not more closely evaluated) degree, the photochemical $A \rightarrow D$ cycloisomerization (19*S*)-**33d** → (19*S*)-**33e** proceeded with *retention* of configuration at ring *D* position C(19).

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[69]) *M. W. Bartlett* and *J. D. Dunitz*, unpublished work [24][29][98]. Note that the presentation **34b** of the X-ray structure of the (racemic) chloro-Cd^{II} complex **34a** (= **23a**; M = Cd–Cl) is depicted in a coil configuration that happens to be inverse to that of the presentation **23b** commonly used in this article for *racemic A*/*D*-secocorrinates after cycloisomerization. For graphical reasons, the same inverted coil configuration is used for the presentation of coil **34c** which would be the one to be assumed for the *enantiomer* of the Cd complex (19*S*)-**33d**. Note further that, in the presentation **34b** of the X-ray structure of **34a**, the methylidene C(20)-atom is labeled as C(24).

[70]) See [102] (there *Fig. 24* on p. 295), and [101] (there *Fig. 29* on p. 161).

4.3. A/D-*Secocorrin* → *Corrin Cycloisomerization of an 1-Oxo*-A/D-*secocorrinate to the Corresponding 1-Hydroxycorrinate.* A/D-*Secocorrin Chromophore Construction by an* A/B + C/D → ABCD *Strategy. Fig. 35* exemplifies what might be referred to as the construction of the corrin chromophore by an $AB + DC \rightarrow ABCD$ strategy. The model system involved happens to be a special case, in so far as the ring *A* in the synthesized secocorrin complex **35e** lacks the methylidene C=C bond at ring *A* and contains on its place a C=C group instead. This allowed the question to be tested, as to whether a Cd^{II} complex of such an 1-oxo (instead of 1-methylidene)-*A*/*D*-secocorrinate will undergo an *A*/*D*-secocorrin → corrin cycloisomerization. This turned out to be the case: chloro-Cd^{II}-3,3,8,8,13,13-hexamethyl-1-oxo-*A*/*D*-secocorrinate **35e**, when irradiated, cycloisomerized to the Cd^{II} complex **35f** of the corresponding 1-hydroxycorrin as smoothly as 1-methylidene analogs afford 1-methylcorrinates, the only qualitatively observed difference to the cases known thus far being the lower reaction rate.

The project described in this section grew out of our investigations on sulfide contractions *via* 'iodinative coupling', specifically from our observation that the *unsubstituted* pyrrolidine-2-thione failed to couple with the ene-lactam **6c** by the method of sulfide contraction *via* 'oxidative coupling' [99]. The finding was a surprise, because it contrasted to the successful coupling of the very same enamide with thiolactam **18b** which bears a CN and three Me groups as substituents (*cf. Fig. 18*). The task of coupling pyrrolidine-2-thione with **6c** became a demonstration of how and why a sulfide contraction *via* iodinative (or more generally, alkylative) coupling can in special cases be preparatively superior to the originally devloped oxidative version. Whereas the treatment of pyrrolidine-2-thione with Bz_2O_2 in the presence of ene-lactam **6c** under standard conditions gave no isolable amount of coupled sulfide **35a**[71]) (*cf.* caption to *Fig. 18*), the iodo derivative of **6c**, ene-lactam **18f**, reacted with the thiolactam in the presence of ^{t}BuOK to afford **35a** in reasonable yield. Subsequent contraction under standard condition (heating with $(EtO)_3P$) smoothly gave the vinamidine derivative **34b**. The bicyclic iodo lactam **21a** was chosen as partner for the coupling with the bicyclic thiolactam **35c** simply because **21a** was already available. The combination defined the goal of the investigation, namely, to seize the opportunity and to check if an 1-oxo-*A*/*D*-secocorrin complex undergoes an *A*/*D*-secocorrin → corrin cycloisomerization.

Coupling and contraction/complexation steps **35c** + **21a** → **35d** and **35d** → **35e**, respectively, proceeded according to plan, the all too moderate yield of the latter step notwithstanding. As a sort of compensation, the final irradiation step **35e** → **35f**, carried out under strictest exclusion of oxygen in benzene, afforded a luscious 89% yield of crystalline chloro-Zn^{II}-1-hydroxycorrinate **35f**. A comparison of its spectral data with those of the chloro-Zn^{II}-corrinate obtained in the 'pacemaker' synthesis (*cf. Fig. 24*) left no doubt about the structure, including the *trans*-configuration of the *A*/*D*-junction included.

The photochemical $A \rightarrow D$ ring closures displayed in *Figs. 33* and *35* are two examples that clearly point to a still largely unexplored scope of the corrin synthesis *via*

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[71]) We presume that the difference is primarily due to the presence of the electronegative CN substituents in the latter (*cf. Footnote 35* and *Part VI* of this series).

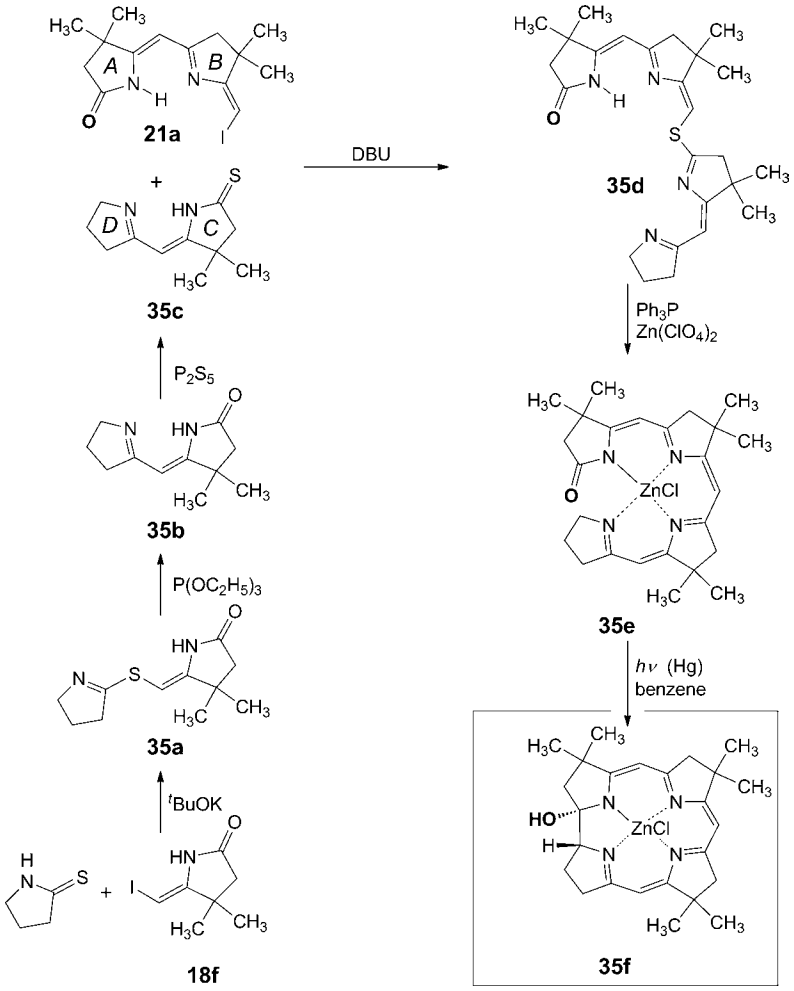
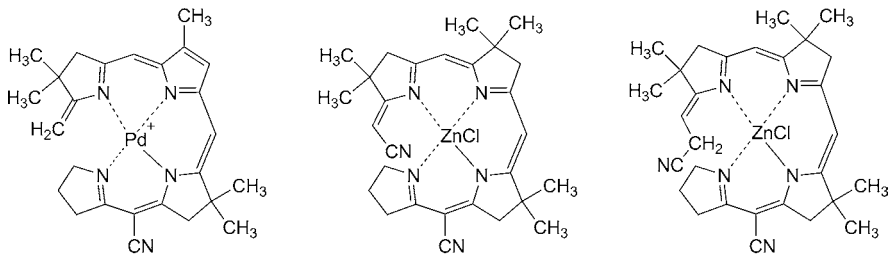


Fig. 35. *Synthesis of the 1*-oxo-A/D-*secocorrin complex* **35e** *by an* A/B + C/D → ABCD *strategy of corrin-chromophor construction and photochemical* A/D-*secocorrin* → *corrin cycloisomerization to the 1*-hydroxy-*corrin complex* **35f** [99].

Reaction conditions [99]: **18f** + pyrrolidine-2-thione → **35a**: ^{t}BuOK, benzene, ^{t}BuOH, r.t.; 60%; **35a** → **35b**: $(EtO)_3P$ in xylene, 130°; 92%; **35b** → **35c**: P_2S_5, toluene, γ-picoline, 130°; 75%; **35c** + **21a** → **35d**: DBU in CH_3CN, r.t.; 49%; **35d** → **35e**: Ph_3P, $Zn(ClO_4)_2$, CH_3CN, 50°; 29%; **35d** → **35f**: *hν*/Hg high-pressure lamp, *Pyrex*, benzene, Ar, r.t.; 89%.



36a **36b** **36c**

Fig. 36. *Further* A/D-*secocorrin complexes that have been shown to undergo the* A/D-*secocorrin → corrin cycloisomerizations* [116][246]. They are pointing to a scope of the ring-closure reaction that may be much broader than explored thus far.

A/*D*-secocorrin → corrin cycloisomerization. In the late 1970s, still other *A*/*D*-secocorrin complexes were studied in our laboratory, the behavior of which point in the same direction. They are the photochemical $A \rightarrow D$ ring closures of Pd^{II}-7,8-*didehydro*-2,2,7,12,12-pentamethyl-*A*/*D*-secocorrinate **36a** (documented in the thesis of *René Nordmann* [116]), and the two *A*/*D*-secocorrin complexes, **36b** and **36c**, studied in exploratory experiments by *K. Srinivasachar* [246] (*Fig. 36*). In **36b**, one of the two H-atoms of the ring-*A* methylidene group of the standard model complex **23a** (M = Zn–Cl) is replaced by a CN substituent, and in **36c** substituted by the NC–CH_2 group[72]). The remarkable finding that both *A*/*D*-secocorrinates could be photochemically cyclized (by strong UV light) in high yields to correspondingly substituted corrinates points to the potential of the *A*/*D*-secocorrin → corrin cycloisomerization of being successful with *A*/*D*-secocorrinates in which the metylidene group at ring *A* may be replaced by any CH–alkylidene group.

5. Concluding Remarks. – The year 1972, when the project of the *chemical* synthesis of vitamin B_{12} had reached its goal, happened to be also the year when research on the problem of the *biosynthesis* of the corrin nucleus of vitamin B_{12} vitamin was taking off in earnest. Back in 1956, the biochemist *David Shemin* [158a] had pioneered the field by showing vitamin B_{12} to be derived biosynthetically from δ-aminolevulinic acid and,

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[72]) *A*/*D*-Secocorrinate **36b** was synthesized from the Ni^{II}-*A*/*D*-secocorrinate **23a** (M = Ni). The reaction with chlorosulfonyl isocyanate afforded a mixture of *endo*- and *exo*-mono-substituted derivatives containing a CN group at the methylidene C(20)-atom (a reaction analogous to the substitution **15d** → **15e**). The synthesis of **36c** also started from **23a** (M = Ni) and proceeded by a substitution reaction at the methylidene C(20)-atom with (dimethyl)(methylidene)ammonium iodide (analogous to **9d** → **14d**), followed by replacement of the Me_2N group by CN with Bu_4NCN. In both syntheses, Ni was finally replaced by Zn. Diastereoisomeric substitution products in both syntheses were separable chromatographically, but yields of pure diastereoisomers were low. The photochemical cyclization of **36b** and **36c** (in benzene under Ar) using a medium-pressure Hg UV lamp proceeded within ¼ h and afforded the corresponding chloro-Zn corrinates in over 90% yields [246]. The motivation for synthesizing the complexes **36b** and **36c** was the preparation of corrin complexes in which the central metal ion could be axially coordinated intramolecularly by a carboxylate group.

in 1963, by incorporation of ^{14}C-labeled substrate, that at least six of the eight peripheral Me groups stem from methionine [158b] (one of those two at ring *C* deriving from the acetic acid side chain). Applying ^{13}C-NMR spectroscopy, *Shemin* finally showed that the seventh Me group, the one located at C(1) of ring *A*, also derives from methionine and (very surprisingly) not from the *meso*-C(20)-atom of urogen III [158c]. This was the state of knowledge in 1972, the chemistry by which microorganisms convert the structure type of urogen III to the corrin ligand, with its unique direct junction of rings *A* and *D*, remaining unknown. At this stage, two prominent natural-product chemists entered the stage: *A. I. Scott* [161][203] at the Texas A&M University and *A. R. Battersby* [162][204] in Cambridge, England. The knowledge we enjoy having today on the marvelous chemical complexity of both an anaerobic and an aerobic pathways of the biosynthetic conversion of urogen III into the corrin ligand of vitamin B_{12} is largely due to the brilliant and fiercely competitive research of these two research groups over two decades between 1972 to the 1990s, work that, at times, was assisted by important contributions of *V. Bykhovski* [205a], *D. Arigoni* [205b], and *G. Müller* [205c]. Significantly, both the Cambridge and the Texan group eventually had to take recourse to the genetic tools of molecular biology [203a] [204a,b] in order to reach the comprehensive insight we have today into the biosynthesis of vitamin B_{12}.

While it is true, of course, that a biosynthetic pathway cannot be uncovered except by studying the biological system itself, chemosynthetic studies on model systems, as well as hypotheses derived thereof, may valuably assist biosynthetic research proper. One of the classical examples is the role the '*biogenetic isoprene rule*' [247] and related model studies on acid-catalyzed polyene cyclizations were playing in the elucidation of the biosyntheses of terpenoids. In the case of vitamin B_{12}, where the chemistry of the novel type of intermediates along the biosynthetic path was largely unknown, the gradual disclosure of the complex natural pathway was progressing in mutual interaction with systematic chemical studies on model structures of potential biosynthetic intermediates [73]. The stupendous directness and ease by which the photochemical *A*/*D*-secocorrin → corrin cycloisomerization had been found to create the *A*/*D*-junction of the B_{12} structure led at the ETH to the conjecture that the vitamin's biosynthesis, in constructing this junction, may also make use of reactivity that is related to such a process [26][28], and that even the very existence of the B_{12} structure as constituent of living Nature may by related to the existence of this type of structure change this reaction achieves [50]. It was such thinking in the aftermath of the B_{12} project that led us to explore the question of whether biocompatible (non-photochemical) variants of the *A*/*D*-secocorrin → corrin cycloisomerization may exist. Extensive 'post-B_{12} studies', carried out in the later 1970s, resulted indeed in the discovery of a whole series of such transformations to the corrin structure *via* non-photochemical $A \rightarrow D$ cyclizations [28][31], including a variant that involves a hydrocorphinate → corphinate *A*/*D*-ring contraction [38][39] as a model of the type of process which eventually emerged as the one on the ways to the *A*/*D* junction in the biosynthesis of vitamin B_{12}. Eventually in the 1980s, these chemical investigations evolved into systematic studies aiming at a chemical etiology of the vitamin B_{12} structure [50][70]: studies toward an understanding – on the level of chemistry – of why the core of this vitamin structure is built the way it is, and not otherwise. The author

discussed these topics extensively in reviews that appeared in 1988 [70] and in 2011 [76]. They are, therefore, not reviewed here again[73]).

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[73]) The experimental details of these studies – at least of those that were carried out by the Ph.D. students and not by postdocs – are to be found in printed doctoral ETH theses, accessible in the Internet under *ETH-e-collection* and the name of the respective author. Author names, together with the general topic of their theses, are listed below: Non-photochemical A/D-secocorrin → corrin cyclizations: *Bernhard Kräutler* [110], *Andreas Pfaltz* [114], *Vittorio Rasetti* [118], and *Silvio Ofner* [120]. Chemistry of corphins und related hydroporphinoids: *Pius Wehrli* [86], *Peter Michael Müller* [100], *Christoph Angst* [119], *Rudolf Waditschatka* [124], *Christian Leumann* [127], *Kurt Hilpert* [123], *René Lattmann* [122], and *Thomas Oberhauser* [132]. Chemistry of uroporphyrinogen octanitriles: *Thomas Früh* [126] and *Christian Lehmann* [128]. Studies towards a chemical etiology of the B_{12} structure: *Kaspar Zimmermann* [130], *Fritz Kreppelt* [131], see also [124][127][132]. Diverse studies on porphinoids: *Beat Zehnder* [121] and *Ulrich Kämpfen* [129]. Chemistry of chlorophylls: *Hanspeter Isenring* [108], *Jean-Luc Luisier* [109], *Engelbert Zass* [111], *Ehrhard Walter* [112], *Bernhard Jaun* [115] and *Rolf Etter* [117]. Chemistry of coenzyme F430: *Alexander Fässler* [125].

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