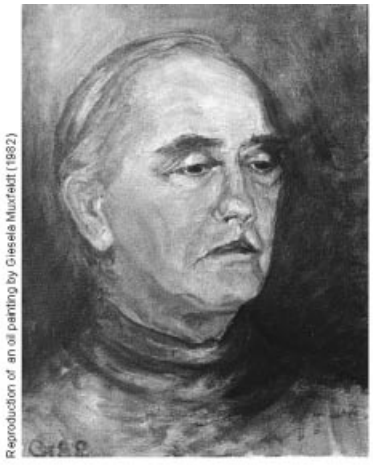

Hans Herloff Inhoffen in His Times (1906−1992)

Gerhard Quinkert[a]

Keywords: Reminiscenses

We can only deal with certain episodes under the chosen title, but it is to be hoped that these may also give the reader some impression of continuity: continuity, that is, in the life of the individual, without regard to the vicissitudes of politics, but also continuity in the sense of a living passage of generations, without the perspective of historical changes. Anyone whose life-span stretched between 1906 and 1992 in Europe clearly experienced unstable times. Three members of the generation succeeding Emil Fischer (1852−1919), working either as biochemists or on questions in medicinal chemistry, each in their own way influenced the scientific development of the young Hans Herloff Inhoffen:

Hermann O. L. Fischer (1888−1960), son of Emil, at the time a *Privatdozent* at Friedrich Wilhelms University in Berlin, assigned the topic for Inhoffen's dissertation.[1]

Walter Schoeller (1880−1965),[2] who had studied a generation earlier at Friedrich Wilhelms University, completing his dissertation (1906) and his thesis for habilitation as docent (1915) under Emil Fischer and engaged after 1919 as a lecturer in the Medical Faculty at Freiburg University, returned to Berlin in 1923 as director of the main laboratory − and substantially as the architect of the international standing as a steroid manufacturer − of what today is Schering AG. A friend of Inhoffen's parents, he was a welcome and enduring influence on the various aspects of the young Inhoffen's scientific development. He proposed Inhoffen's *Doktorvater*, recommended Windaus's Allgemeines Universitätslaboratorium in Göttingen and then Sir Charles Dodds's Courtauld Institute of Biochemistry in London for postdoctoral study, and in 1935 arranged for Inhoffen to work in synthesis in the main laboratory at Schering AG, from 1941 onwards as department head.

Adolf Windaus (1876−1959),[3] initially a student of medicine in Freiburg and Berlin, had acquired an interest in the chemical problems underlying physiological processes thanks to Emil Fischer, for whom he would later work as an assistant. After completing a dissertation on cardiotoxins of the digitalis family at the Medizinisch-chemisches Laboratorium at Freiburg University under the supervision of H. Kiliani and in 1903 received the *venia legendi* on presenta-

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tion of his *Habilitationsschrift*, he was called to a chair at Göttingen, as the successor to Otto Wallach, in 1915.

In the early 1930s Inhoffen spent four fruitful years as an assistant with Windaus, thanks to Schoeller's patronage. At that time, steroid chemistry stood at the zenith of the development of natural products chemistry, with a deepening impression forming that cholesterol, a prominent representative of the sterols, occupied a central position in the complex network of the steroids and their diverse subclasses.(1) The elucidation of the constitution of cholesterol had been the declared aim of numerous investigations from the beginning of the 20th century. In 1903, Adolf Windaus presented the first findings, in *Über Cholesterin.*[4] In the same year, Otto Diels and Emil Abderhalden reported *Über den Abbau des Cholesterins.*[5] The following period saw many attempts to apply individual experiments to the acquisition of pieces of partial structural information, which would at some future point require piecing together detective-style to form an overall picture. Windaus's 1919 finding[6] that cholanic acid was accessible through oxidative degradation both from coprostane (and hence from cholesterol) and also from cholic acid (and hence from a bile acid) acted as a bridge between sterols and bile acids, the chemical nature of which had been the subject of studies by Heinrich Wieland[7] beginning in 1912.

The establishing of the relationship between sterols and bile acids was a great advance, as now findings made on representatives of one class were also benefiting to members of the other class. In Göttingen, moreover connections were being corroborated between sterols and various steroids that were not bile acids. In 1928 Windaus[8a] had received the Nobel prize for chemistry *for the services rendered through his research into the constitution of sterols and their connection with the D vitamins.* Wieland at the same occasion was awarded the 1927 Nobel prize for *chemistry for his investigations of the constitution of the bile acids and related substances.*[8b] The hypothetical partial formulae used in both Nobel lectures (Scheme 1), though, were to require fundamental revision four years later.(2)

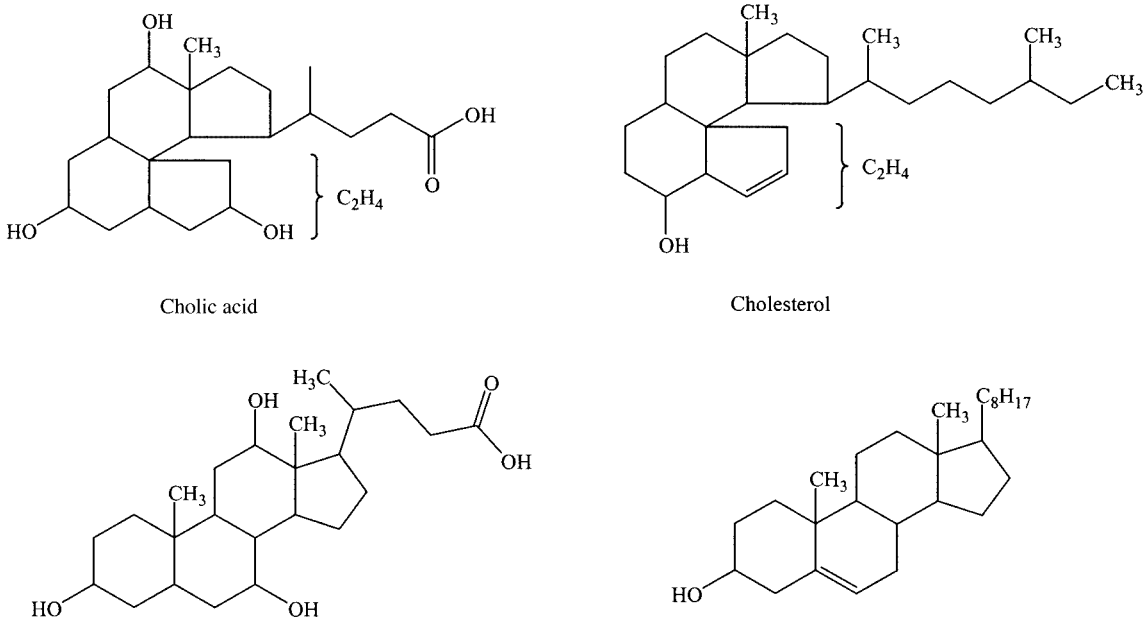
Dissent regarding the partial formulae used as working hypotheses by Windaus and Wieland was coming from very different directions.(3) One faction was driven by the desire to replace, as much as possible, the abundance of pieces of information acquired from locally restricted partial actions and their need to be replaced by some globally extended total action, which would then provide information on the underlying molecular skeleton. Leopold Ruzicka[10] had already used such a strategy for the constitutional elucidation of the sesquiterpenes in 1921. It had involved the use of dehydrogenation techniques, which provided easily identifiable aromatic hydrocarbons containing the overwhelming majority of the carbon atoms present in the hydroaromatic precursor. Working wholly by this approach, Otto Diels[11] had obtained the aromatic hydrocarbon chrysene (Scheme 2) by dehydrogenation of cholesterol with palladinized charcoal. Because of the high temperatures at which the dehydrogenation had had to be carried out and the impossibility of ruling out skeletal rearrangement under these conditions, Diels and others hesitated to draw direct immediate conclusions relating to the underlying molecular structure from this observation. Otto Rosenheim and Harold King[12] had fewer scruples, and assumed a condensed ring system corresponding to that of chrysene for sterols and bile acids. They did so with strong support from John Desmond Bernal,[13] who had established by X-ray structural analysis that molecules with the Windaus–Wieland partial constitution would not fit in the experimentally determined unit cell. Diels[11d] now once more took centre stage. He had developed a dehydrogenation technique that made use of selenium, which took place at a significantly lower temperature than dehydrogenation with palladium on carbon. This technique produced an additional hydrocarbon identifiable (albeit only later and elsewhere) as 3-methylcyclopentenophenanthrene (Scheme 2).[14] This so-called *Diels hydrocarbon* offered persuasive support for the constitution proposed by Rosenheim and King. Once Wieland and Elisabeth Dane[15] had succeeded in satisfying themselves that the Blanc rule(4) originally used for the determination of sections of the Windaus-Wieland formulae might have exceptions in cases in which substituents might give rise to ring strain, and so did not necessarily allow infallible determination of the size of carbocyclic rings, they too departed from the original partial formula in favour of the modern generally recognized steroid formula (although with the five-membered ring D rather than chrysene's six-membered one).

In 1932, in a comprehensive account entitled "*Über die Konstitution des Cholesterins und der Gallensäuren*",[17] Windaus critically re-evaluated his earlier experiments and their associated interpretation, accepting the now generally recognized formulae.

In the mid-1920s Windaus enjoyed world-wide recognition as the most authoritative expert on sterols. It was therefore no surprise when in 1927 he was invited to work on sex hormones by Schoeller of Schering AG, even though the steroidal natures of the molecules in question had not been anticipated at all. Windaus entrusted the collaboration with Schering to his assistant Adolf Butenandt. He himself had already accepted another invitation two years previously from the New York physiologist Alfred Hess to work on the anti-rickets agent vitamin D, produced by UV irradiation of a provitamin.[18] Vitamin D, provitamin D and what was to prove to be the extremely complex chemical relationship existing between them thereafter had precedence over all other problems in Windaus's laboratory.

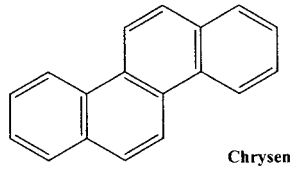
The experimental investigations were broadly defined and were carried out with the aid of a considerable staff. In their best-seller *Steroids*, the Fiesers[19] list 55 team members just from Göttingen who over the years contributed experimental findings involving the structures and functions of vitamin D and provitamin D.(5) Inhoffen is also included in this group. An important publication from this time is his 1932 report *Über das Neoergosterin*.[20] The confusingly named "Neo-ergosterin" had been unexpectedly prepared as early as 1928.[21] High-vacuum distillation purification of a photocondensation product obtained on irradiation of provita-

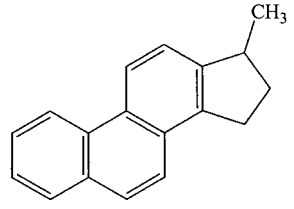
Wieland–Windaus constitution formulae



Wieland–Rosenheim constitution formulae

Scheme 1





Scheme 2

min D_2 with visible light in the presence of eosin and with exclusion of oxygen had resulted in a fragmentation, affording the aromatic[22] neoergosterol with extrusion of CH_4 (Scheme 3). The originally assumed partial constitution, with an aromatic ring C,[20] was finally abandoned in favour of one with an aromatic ring B.[23] The highly unsaturated nature of ring B, though, applied not only for neoergosterol, but also for ergosterol itself,[24] the constitution of which was thus definitively established.

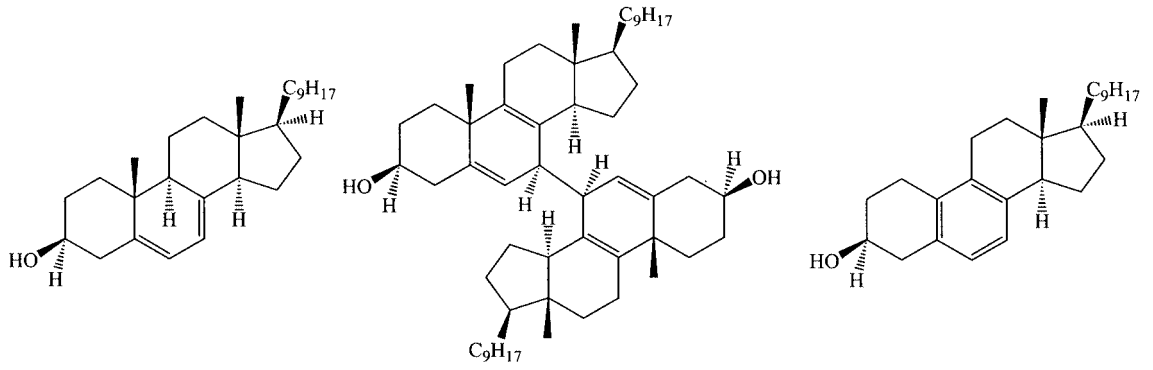
Inhoffen[25] had thus established a structural connection between neoergosterol, with its aromatic ring B, and the photocondensation product, and Owades[26] consistently interpreted the photocondensation as a dimerization proceeding through radicals.

The fact that ergosterol and 9α-lumisterol(6) reacted to afford the corresponding photocondensation product, while 9β-ergosterol(6) and lumisterol did not (Scheme 4)[27] suggested that the triplet spin isomer(7) of eosine preferentially abstracted the H-atom at C(9) for stereoelectronic reasons. With the aid of the two rules.

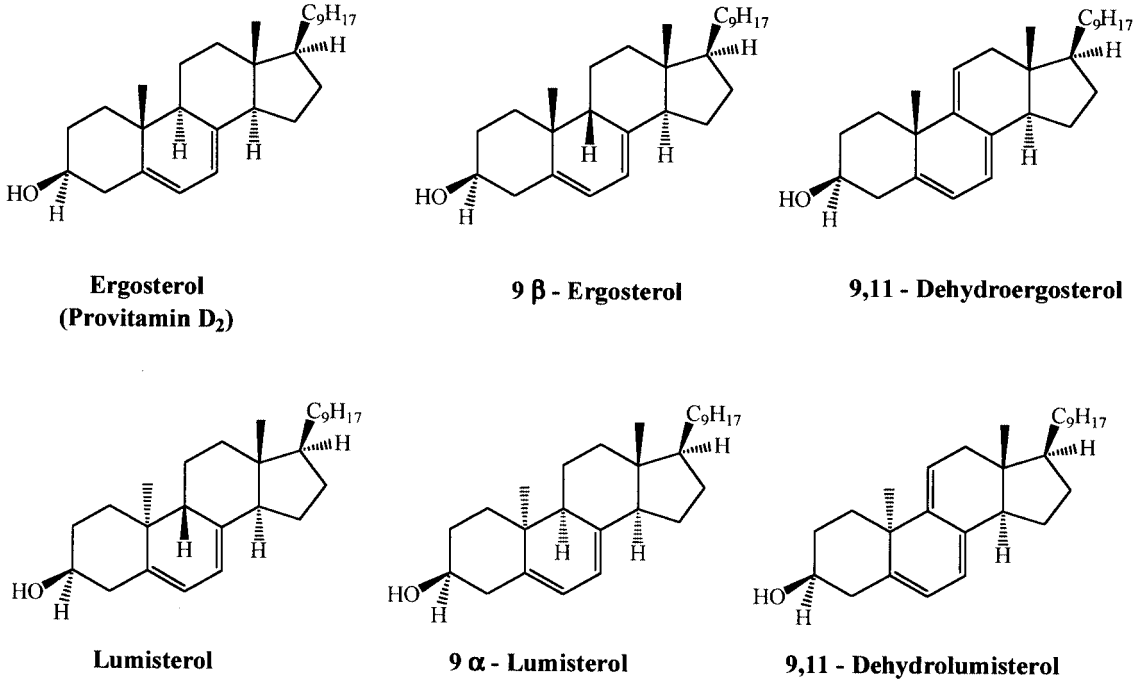
- Photocondensation products are only produced from those (5,7)-steroid dienes that possess H_α on C(9), and
- Mercury acetate-assisted dehydrogenations of ergosterol and 9β-ergosterol resulted in 9(11)-dehydroergosterol and those of lumisterol and 9α-lumisterol in 9(11)-dehydrolumisterol

it was possible for the configurations at C(9) and C(10) in ergosterol and its three stereoisomers to be fixed conclusively. In like or similar manner, knowledge of the constitutional relationships was also extended to stereostructural details in other steroid representatives.

By and large, steroid chemistry now appeared to have been "done." Two monographs published in 1936[29,30] did nothing to contradict this impression. The structural edifice of steroids towered like a monolith over the landscape of organic chemistry for the second third of the twentieth century. Movement was only to return to the scene with the



Scheme 3

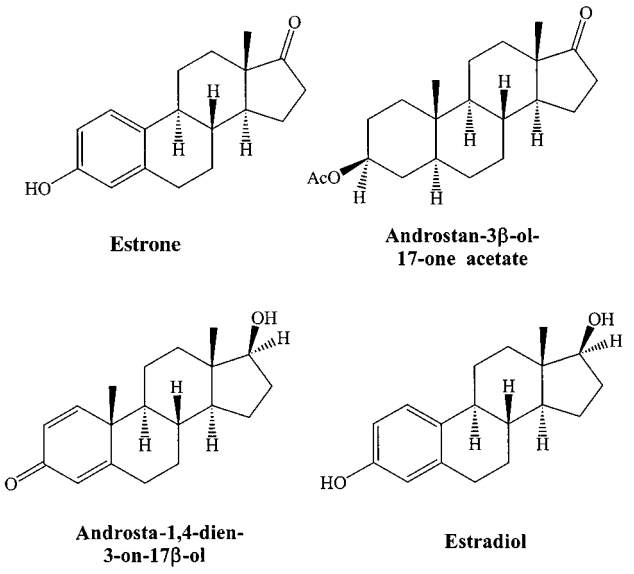


Scheme 4

rise of conformational analysis[31] and the steroid syntheses it encouraged. Steroid total synthesis had been tangentially touched on both by Wieland[9] and by Windaus[8] in their Nobel lectures, and held to be at best achievable in some far future. Ambitions towards to the first attempts at total synthesis, though, were already finding believers in the next generation, both in Munich[32] and in Göttingen,[33] though it soon became apparent that these synthetic efforts were still far from the goal.

Towards the end of his time in Göttingen, Inhoffen became taken by the desire of making medicinally useful steroids accessible through partial synthesis. As his first target molecule he naturally thought of estrone, the constitution of which had been put forward by Butenandt in 1932.[34] That Butenandt's estrone formula had the four rings[(8)] of the steroid skeleton, one of them − ring A − aromatic (Scheme 5), was not in doubt. Inhoffen's work on the aromatization of ergosterol to neoergosterol (by way of the photocondensation product) had provided intellectual impetus for selective aromatization of ring A in other suitable precursors. The specific constitutional element of a non-conjugated cyclohexadiene with a CH_3 group in an allyl position was recognised as a constitutional prerequisite for thermally induced aromatization with extrusion of this methyl group. In relation to estrone, with its aromatic ring A, a steroid with a partial constitution incorporating a cyclohexa-1,4-dien-3-one would be desirable (Scheme 5). To this end, methods for partial dehydrogenation of the steroid ske-

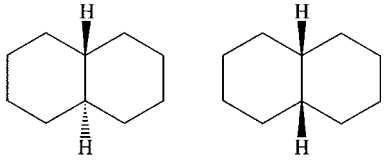
leton required development. Quite a few laboratories applied themselves to this challenge. Not Windaus's of course, since work with sex hormones had been entrusted to Butenandt. For a number of years Butenandt and Inhoffen were in competition to see who might succeed in the first partial synthetic preparation of estrone from an inexpensive sterol. Looking back in 1942, Butenandt sportingly judged that it had been Inhoffen's − now working in Schering AG's Berlin laboratories − contribution that had resulted in the transformation of 3β-Hydroxy-5α-androstan-17 one acetate, accessible from cholesterol, into estradiol by way of 17β-Hydroxy-androsta-1,4-dien-3-one (Scheme 5) and thus attained a remarkable and long-sought goal.[35] This provided grounds for Windaus to invite Inhoffen to apply for habilitation in the Mathematisch-Naturwissenschaftliche Fakultät in Göttingen's Georg-August Universität. The title of *Dr. phil. habil.* may be assumed to have greatly assisted Inhoffen some years later in the transition from the industrial to the academic career ladder.



Scheme 5

The steroid dienones needed for the selective aromatization of ring A were obtained in a two-step procedure: bromination of a 3-keto steroid and subsequent dehydrobromination. Neither step of the process was by any means immediately successful. Whether the initially produced brominated component has bromine at C(2) or C(4), and in the β- or the α-position, depends on the nature of the junction between rings A and B (*trans* or *cis*) and also on the type of reaction conditions (irreversible or reversible reaction course) used.

The question of such *cis-trans* isomerism in condensed ring systems had garnered interest in the Göttingen laboratories with the observation that cholest-4-ene was transformed into cholestane on catalytic hydrogenation under acid conditions, but into the C(5) stereoisomer coprostane under neutral ones.[36] Through these experimental observations, Windaus came to sympathize with Hermann Sachse's[37] and Ernst Mohr's[38] ideas about the non-planarity of the cyclohexane ring. Just as Emil Fischer had used the strain-free tetrahedron as a building block for strain-free aldohexoses and observed agreement between the experimentally obtained and theoretically expected number of stereoisomers, Windaus anticipated two non-strained stereoisomers with the constitution of decalin (Scheme 6). He was able to persuade his student Walter Hückel to address the *cis-trans* isomerism in decalin experimentally for a habilitation project. Hückel prepared the two *cis* and *trans* isomers,[39] thus unavoidably coming down against Adolf von Baeyer's postulated dogma of the planar cyclohexane ring. From this time on Hückel viewed Adolf Windaus as a natural products chemist who always allowed himself to be guided by the results of experimental observation, while on the other hand attempting to make his young colleagues open to problems of theoretical organic chemistry. Hückel turned a deaf ear to Windaus's advice to familiarize himself with the methods of X-ray structural analysis, however, thereby missing the opportunity to pursue the order of stabilities of stereoisomeric chair and boat conformations and the consequences of the existence of equatorial and axial bonds in every methylene group in the chair conformation of cyclohexane in greater detail.



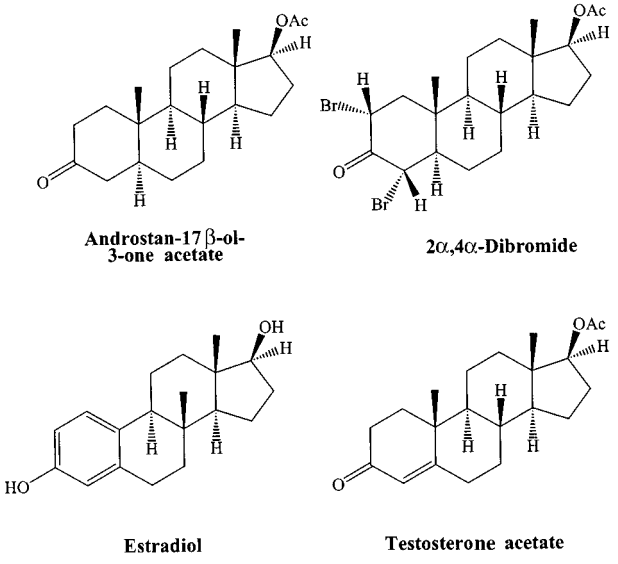
Scheme 6

The receptiveness towards problems of theoretical organic chemistry mentioned above was kept within rather narrow limits among chemists in the first half of the twentieth century. In the second half this was to change appreciably. It required a new perspective, opened up to all chemists by Barton's conformational analysis.[31,40]

A demonstration case of how the use of particular rules can aid in the blazing of trails through the experimental jungle is provided by the bromination of 3-keto-steroids. The first patterns were recognized by Butenandt[41] in the mid-1930s. If there is a *trans* junction between rings A and B, C(2) is brominated preferentially, while in the presence of a *cis* junction bromination mainly takes place at C(4). The second rule was proposed only in the 1950s, by E.J. Corey,[42] bringing clarity into the by now extensively investigated field: primary bromination products contain their Br atoms in axial orientations, secondary products in equatorial orientations. Since the relationships between conformation and configuration in steroids are unambiguous, thanks to the impossibility of complete inversion of the entire four-ring system, the configurations of primary and se-

condary products can therefore be predicted according to these rules. Where there are rules, however, there tend to be exceptions. Carl Djerassi[43] was able to demonstrate in a detailed analysis in 1960 that − in cases involving Newman strain(9) − bromination in ring A of a steroid was not compelled to take place in the half-chair conformation, but could also proceed in the half-boat conformation, with the formation of a primary product containing the new bromine atom in an equatorial orientation.

After extensive investigations by Inhoffen, first with Huang-Minlon and then with Zühlsdorff[45] in the cholestane and androstane series, the partial synthesis of estradiol from 17β-Hydroxy-5α-androstan-3-one acetate (Scheme 7) was carried out at Schering AG.[46] The 2α,4α-dibromide obtained by bromination was dehydrobrominated by treatment with technical collidine as established by Butenandt.[47] Acetate hydrolysis and homolytic cleavage of the angular CH_3 group at C(10) through pyrolytic aromatization in the presence of tetralin as hydrogen donor then afforded estradiol. The originally selected conditions, with a batch reaction procedure, were still technically very primitive and the chemical yields obtained were unacceptable. Both were to change over the course of time, thanks to extensive process development. The use of higher temperatures, continuous reaction procedures and brief exposure periods, with a dilute solution of the pure 2,4-dibromide being sprayed into the high-temperature zone of a quartz apparatus, were finally to lead Inhoffen and Zühlsdorff to products from which the target hormone could be isolated in constant chemical yields of nearly 60%.[48]

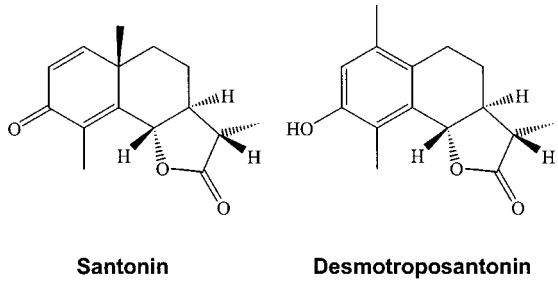


Scheme 7

The published findings from Schering's Berlin main laboratory during the 1930s and 1940s rapidly drew attention, especially in other industrial laboratories. The pyrolytic aromatization procedure was paid particular attention in a 1947 US military government report on synthetic hormones in Germany.[49] The procedure had to be further elaborated in greater detail where it was applied, however. Hershberg and his colleagues at the Schering Corporation[50] offer one celebrated example. Djerassi and his co-workers at Syntex also made intensive use of Inhoffen's pyrolytic aromatization,[51] supplying a particularly attractive example in their preparation of estradiol from testosterone acetate (Scheme 7).[52]

The blossoming of steroid chemistry, the growing importance of steroid synthesis in academia and industry and, not least, the role of the protagonists have since around 1990 been the subject of some in-depth meditations.[53] In the history of biologically active agents, as described by those directly involved, it is not uncommonly the case that the witnesses closest to the events do not necessarily speak with the greatest reliability. "*There are some instances of disagreement, some errors and what appears to be some bias in some of these accounts; several authors had an iron in the fire. There was both open and behind the scenes competition and the opportunities for reward in terms of financial gain and public as well as scientific acclaim were great. There are some informational gaps in the story and that is to be expected in view of the major role played by commercial interest*".[54]

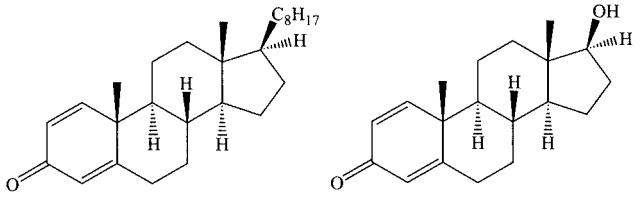
As we have seen, the pyrolytic rearrangement of the photocondensation product obtained from ergosterol into neo ergosterol inspired Inhoffen in further transformations of steroids with 1,4-diene-3-one partial constitutions into those phenols with one C-atom and two H-atoms fewer than the original keto-steroids. The known literature example of an acid-catalysed isomerization of the sesquiterpene santonin into desmotroposantonin[55] (Scheme 8) encouraged him to attempt an analogous aromatization with steroidal 1,4-diene-3-ones.[56a]



Scheme 8

Indeed, cholesta-1,4-dien-3-one and 17β-Hydroxyandrosta-1,4-dien-3-one (Scheme 9) each gave an isomeric phenol in good chemical yield on treatment with sulfuric acid in acetic anhydride at room temperature.[56b] Djerassi, in his dissertation carried out under the supervision of A. L. Wilds, confirmed the acid-catalysed rearrangement in the cholestane series.[57a] He introduced the handy term *dienone-phenol rearrangement*, which can be looked upon as a *Wagner−Meerwein* rearrangement resulting in a 1,2-shift of the CH_3 group. 1,2-Shifts of CH_3 groups could be unambiguously confirmed in two cases,[57b,57c] though not in those

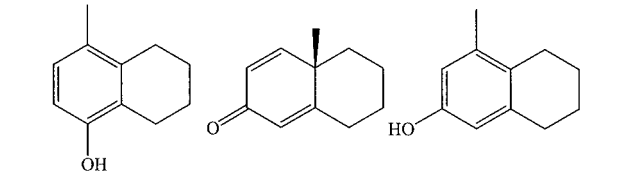
cases envisaged by Inhoffen for the production of steroids with an aromatic ring A and a CH_3 group at C(1).[56] R. B. Woodward and T. Singh[58] had doubted the constitution of the phenolic rearrangement product from 17β-Hydroxy-androsta-1,4-dien-3-one assumed by analogy from the phenolic desmotroposantonine, because there was no estrogenic activity and the isolated product behaved like a cryptophenol. Woodward, Inhoffen, and their co-workers[59] were able to establish through identification of a product obtained by selenium dehydrogenation that in this case a more profound skeletal rearrangement rather than a 1,2-shift had taken place in the acid-catalysed dienone-phenol rearrangement.



Cholesta-1,4-dien-3-one **Androsta-1,4-dien-17β-ol-3-one**

Scheme 9

As a general reaction type, the dienone-phenol rearrangement has two different reaction channels, leading to constitutionally isomeric phenols. The initial impression of an "*either-or*" situation soon had to be modified to "*not only-but also.*" Still more importantly, the reaction conditions applied − the presence or absence of water[60a] − determine the degree to which the population of reacting dienone molecules is distributed between the two reaction channels leading away from the common origin. W. H. Hopff and A. S. Dreiding[60b] found that 1,2,3,4,6,9-hexahydro-6-oxo-9-methylnaphthalene (Scheme 10) gave a phenol mixture in which the skeletal rearrangement component was present in a proportion of 80% and the CH_3-shift component one of 20% on treatment with sulfuric acid in acetic anhydride, whilst the ratio of the two phenols was reversed when aqueous mineral acid (30−50%) was used to initiate the dienone-phenol rearrangement.[60b]



rearrangement **1,2-methyl migration**

Scheme 10

In retrospect it can be said that the acid-induced dienone-phenol rearrangement is more of academic importance, as an example case for reaction mechanism studies making it clear that chemistry cannot only be learned by rote but also understood.[61] (10) The pyrolytic aromatization of ring A in steroids, in contrast, is used industrially to this day.

At the beginning of the 1990s, Schering AG offered to inaugurate and participate in an annual *Inhoffen Lecture* at the Technische Universität Braunschweig, where Inhoffen had been active for over thirty years. Henning Hopf(11) not only eagerly took up the suggestion, but was also successful in persuading the *Gesellschaft für Biotechnologische Forschung* (*GBF*) in Braunschweig to endow an *Inhoffen Medal*. Since 1994, the H. H. Inhoffen Lecture has been a joint event organized by the Technische Universität *Carolo Wilhelmina* and the *GBF*, at which the invited speaker is awarded the H. H. Inhoffen Medal. Rudolf Wiechert, formerly Director of Research in Chemistry and Molecular Biology at Schering AG, justified the proposed Inhoffen Lecture as a permanent reminder to the younger generation both of Inhoffen and of his two fundamental achievements at Schering AG.[62b] One of these two achievements, naturally, was the 1937 pyrolytic aromatization.[25] That had originated − as outlined in detail above − by analogy from a related observation and was to become the key reaction in the partial synthesis of 1,3,5(10)-estratriene derivatives. The other has to do with the 1938 discovery that steroid hormones possessing a keto group at C(17) are also biologically active on oral application after ethynylation.[56a] What is now a basic assumption, immediately recognized as crucial in hormone therapy and a number of years later for the development of oral contraceptives, was a matter of pure chance.(12)

Inhoffen's last report from the Schering laboratories dates from 26 December 1944. It is included in a letter to Walter Schoeller, who had been driven out of Berlin by the bombing and was not to return there. "*We have struggled through the estradiol battle of 1944 with a result of 15 kg*," it reads. Inhoffen also soon left Berlin; by the end of April 1945 the frontline was running through the Müllerstrasse plant. At the end of May the Russian occupiers' dismantling of the still existent production facilities began. Schering's patents and trademarks were open for the use of all.[65] Three patents appropriated by the US government were later sold on to the Syntex Corporation.[66]

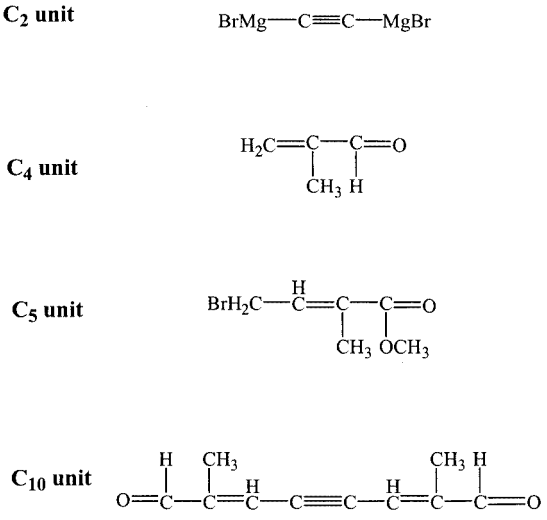
Inhoffen's 26 December 1944 letter to Schoeller ends with the rather cryptic "*We have just come by some highly effective crystalline Vitamin A acid.*" Following up of further clues in the chemical literature gives the following picture. During the German occupation of the Netherlands in 1943−1944 there was an enforced collaboration between the chemists J.F. Arens and D. A. van Dorp of Organon in Oss and Inhoffen of Schering in Berlin[53b,67b,68a]. Inhoffen supervised and directed the work of the Dutch researchers, which was to lead to, among other things, vitamin A-acid. This collaboration ended with the severance of relations between the Netherlands and the German Reich. A common publication of the results was unimaginable, so the Arens/van Dorp group (Organon)[67] and Inhoffen(13) and later co-workers (Technische Hochschule Braunschweig)[68] each published independently.

The contribution to carotenoid synthesis originating from Braunschweig is considerable. Between 1948 and 1955,

38 original publications and two reviews were published. The majority of reported syntheses for symmetrical target compounds follow a strategy, either in the beginning or at the end of the construction of the C-skeleton, of a condensation between two aldehyde groups, either of one and the same component or of two separate molecules, with acetylene. The resulting diols are dehydrated to the fully conjugated dehydro target compounds with a central triple bond. The triple bond acts like an isolator on the reactivity of the molecule, preventing unwanted rearrangements. It may be partially hydrogenated to the polyene with a central *Z*-configured C=C-bond with the aid of the *Lindlar* catalyst developed at Hoffmann-La Roche in Basel. In this way a stereoisomer with physical and chemical properties of interest to synthetic chemists is obtained, and its chemical conversion into the envisaged target compound with a central C=C bond of *E* configuration can comfortably be achieved. This procedure was used by Otto Isler and colleagues[69b] for optimization for industrial production of β-carotene by Inhoffen's $C_{19} + C_2 + C_{19}$ [69a] *Aufbauprinzip* (Scheme 11).

Inhoffen and Isler and their co-workers communicated their synthesis of the food colorant dimethylcrocetin[70] according to a $C_4 + C_2 + C_4 = C_{10}$; $C_5 + C_{10} + C_5 = C_{20}$ *Aufbauprinzip* in a joint publication (Scheme 12)(14).

The collaboration between the Institute of Organic Chemistry in Braunschweig and the scientific laboratories of Hoffmann-La Roche & Co. AG in Basel was formally sanctioned. This was much appreciated in Inhoffen's group, provincialism prevailing for a number of years after the Second World War in Germany gradually began to dwindle away. Collaborative ventures of this sort were judged rather differently by West Germany's chemical industry, engaged in restructuring and reacquisition of economic competitiveness,

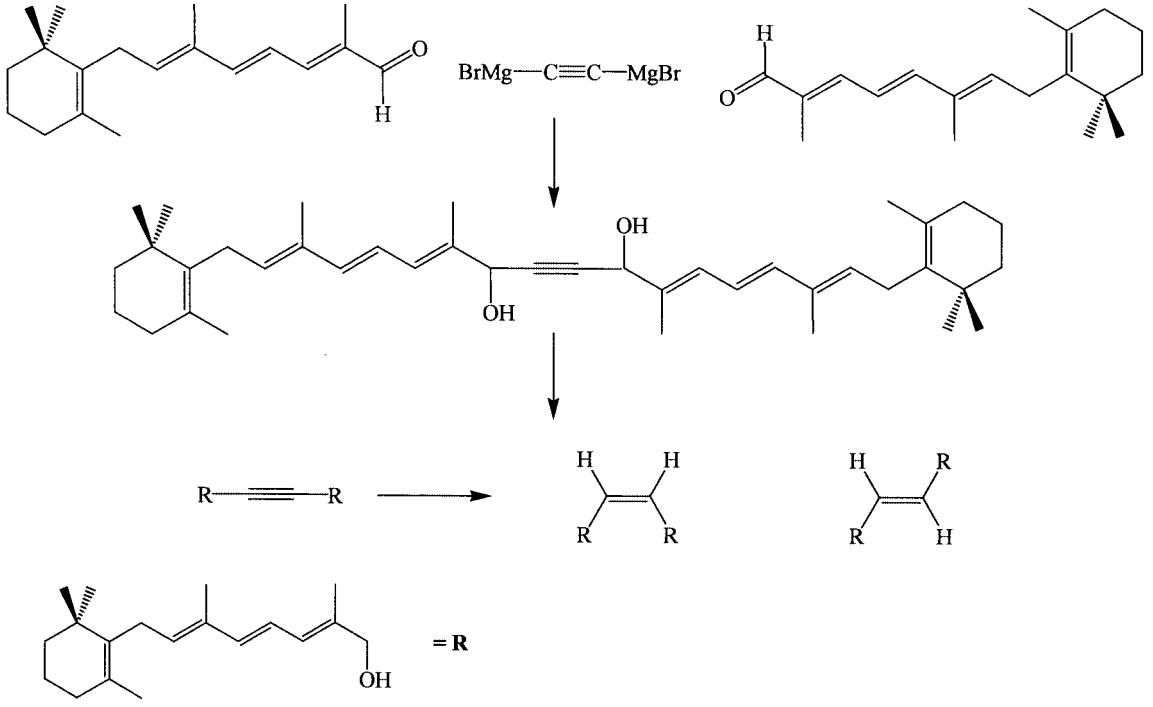


Scheme 12

because of the fear that they could lead to large-scale migration of German scientists abroad.

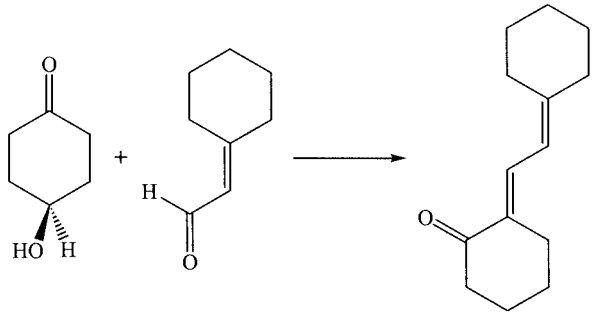
Hence, for example, at the fifth Kuratoriumssitzung of the *Fonds der Chemischen Industrie* on 13th July 1951 in Ludwigshafen it was decreed that *University teachers with collaborative contracts with foreign companies would not receive funding*.[71] (15)

In contrast with the partial synthesis of estrone and the total synthesis of β-carotene, in which the authors had had an eye to industrial application, the efforts towards the total synthesis of one of the D vitamins beginning in the mid-1950s were more of academic significance: a successful synthesis as evidence for the correctness of the interpretation



Scheme 11

of the structure of the envisaged target compound.[28c] The first publication within a series of papers, with the understated title *Studien in der Vitamin D-Reihe,*[72] began with the announcement to carry on Göttingen's vitamin D tradition in nearby Braunschweig. The Göttingen tradition in this context, by the way, included not only Windaus's investigations into the irradiation products of ergosterol, but also the *Synthetic Experiments in the* P*reparation of Anti-rickets Vitamins* undertaken in Göttingen by Karl Dimroth shortly before the Second World War. In the first four communications[73] Dimroth presents a plan based on model studies of how he intends to construct the conjugated triene system of the target compound: through an aldol condensation between 4-hydroxy-cyclohexanone (initially) with cyclohexylidenacetaldehyde(16) (Scheme 13) to afford a dienone in which the (C=O) group should later be replaced by the (C=CH_2) group.



Scheme 13

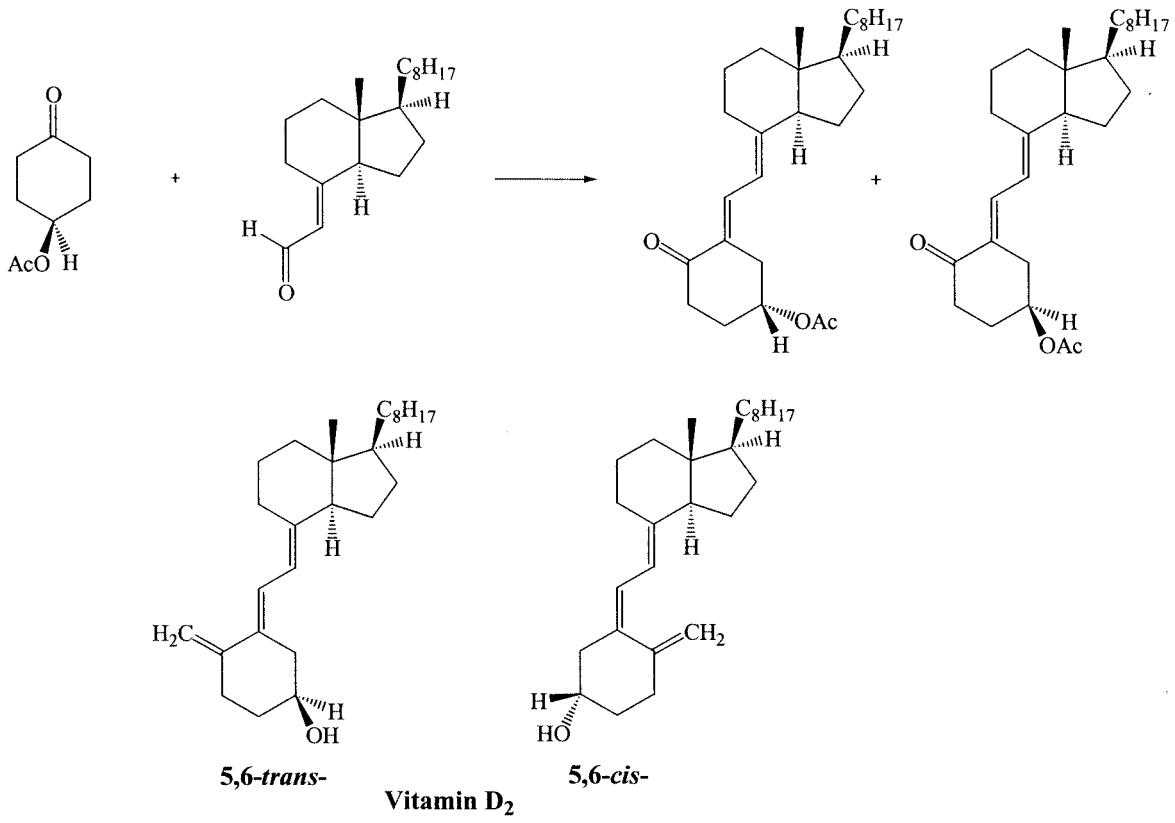
This synthetic approach is so simple that it is hardly surprising that it was also chosen, or was soon willingly adopted, by other workers. Aldersley and Burkhardt[74] set out independently of Dimroth on the same synthetic route at the same time. Sixteen years later, Inhoffen, Brückner and Gründel[72] followed up Dimroth's basic concept, but this time no longer in exploratory fashion, with exchangeable model compounds, but on the far more challenging exhibition ground, with use of the so-called C_{20}-degradation aldehyde from vitamin D_3 and 4-acetoxycyclohexanone as condensation components (Scheme 14). The Braunschweig chemists would have failed, just like all their predecessors, in the installation of the exocyclic methylene group on the future ring A had they not had the good fortune of being able to apply the just published Wittig reaction for their purposes.[76]

Once the total synthesis of vitamin D_3 had been achieved, Inhoffen confirmed retrospectively that *without the Wittig reaction there would have been no complete vitamin D synthesis before us today.*[77] The meaningfulness of this statement is made all the clearer if account is taken of the fact that the Wittig reaction was used three times in total during the Braunschweig vitamin D_3 synthesis. Another peculiarity of this synthesis lies in its lavish use of relay molecules.[28c] It was enormously helpful to have as many of the intermediate compounds on the synthetic pathway as possible available (through degradation of the naturally occurring target compound) before their actual synthesis, as this facilitated their isolation and identification during the ensuing synthesis. A synthesis operating with relay compounds also alloweds synthetic steps to be performed in parallel, while in a conventionally executed synthesis they would have had to be carried out one after the other. The case at hand is a demonstration example: seven relay compounds were used! Only three of them had already been known; the remaining four were produced through degradation specially for the synthesis.[78] The total synthesis with the incorporation of the side chain was completed.[79]

In 1961 the Gesellschaft Deutscher Chemiker awarded Professor Inhoffen the Emil Fischer Medal: in recognition of his outstanding achievements in the field of the synthesis of the important natural substances estrone, β-carotene and vitamin D and his successful effects as an academic teacher.[80] The mention of his successful teaching is more than a politesse. To have first class chemists from every generation available stabilizes the industrial production factor called "knowledge." As a rule, this requires the existence of a personal relationship between a successful University teacher and the head of research at a chemical company. In Inhoffen's case there was scarcely any deficiency here. The best of his students who wished to pursue industrial careers distributed themselves very evenly over the most varied organizations: Horst Pommer went to BASF, Klaus Weissermel to Hoechst, Gerhard Raspé to Schering, Hans-Jürgen Hess to Pfizer, Klaus Brückner and Klaus Irmscher to Merck, Siegismund Schütz to Bayer, Hans Schäfer to Degussa, Jürgen Engel to Asta-Medica.

In the mid-1950s a certain concentration became evident. The reason for this was a 1954 agreement intended to bind the University professors Inhoffen, J. Kimmig, A. Lüttringhaus and C. Schöpf, as a team, more closely to Merck in Darmstadt. This professorial consulting team was to evaluate ongoing research at Merck, make proposals for restructuring of in-house research and provide above-average young professional chemists. At the Braunschweiger Institut für Organische Chemie, those who made their way to Darmstadt qualified as "merkwürdig" (remarkable). The very few who were able to chose between Merck and Hoechst were viewed as "hoechst merkwürdig." Its evident success notwithstanding, this unusual arrangement lasted only six years, the interesting experiment in hybrid industrial management being brought to an end by animosity, perhaps predictable from the beginning, between internal and external direction of research. Questions relating to the conditions that must have been met in the Braunschweig organic chemistry institute, to explain the relatively high proportion of future successful industrial chemists, reveal little in the way of clear answers.

Inhoffen was well aware of the effect he had on others. This was unmistakable even on the first encounter. If one had dealings with him more frequently, the impression that grew was that he would only get along harmoniously for prolonged periods with those who would neither obey unquestioningly, but nor deny him − in fact or supposedly −



Scheme 14

the necessary respect. Otherwise, what he expected of his co-workers could be summarized as: don't talk, do; if talking is unavoidable, then only after careful consideration; in contradicting or grasping initiatives that would be up to the "*Chef*," then it would be advisable to have checked whether you were right and would in all probability remain right. All in all, a miniaturized model of the community in which preparation for the "grown-up world" took place. Chemistry necessary for solving of set tasks, one to a large extent could − in fact had to − pick up for oneself. A playpen for autodidacts, especially for those with the luck of the diligent on their side. In the experiments carried out and their interpretation there were no concessions. Inhoffen was known for rapidly being able to identify the weak points of an experiment. As a star witness it is possible to cite R. B. Woodward, who commented, "*I knew well that my friend Hans Herloff Inhoffen was among the most scrupulous and careful of experimentalists*".[81]

To avoid extending this biographical sketch unduly, we will not go into the series of scientists each of whom habilitated as a privatdocent in Inhoffen's Braunschweig institute. With one exception: Hans Muxfeldt, recommended to Inhoffen, then in search of a habilitand, by Göttingen's Hans Brockmann. As was soon to become obvious, Muxfeldt was able to thrive in Braunschweig. He participated in the model experiments begun by Inhoffen in the synthesis of tetracyclins[82] and in 1958 submitted a thesis for habilitation as docent on the *Synthesis of Tetracyclic Degradation Products of Anhydrotetracyclins*. To anyone who read this work and the later publications from 1959 to 1968[83] it quickly became apparent that Muxfeldt was playing in a different league. Inhoffen also took account of this: for one in that he would take Muxfeldt with him to the regularly held discussions with representatives of the pharmaceutical divisions of Hoechst or Merck on the development of synthetic antibiotics, and then when in 1960 he gave what had previously been the joint topic of the *Total Synthesis of (+)-Terramycin* over to Muxfeldt alone. Hans Muxfeldt received attractive offers from the USA (first from the University of Wisconsin, Madison and some years later from Cornell University in Ithaca), which he accepted. Before he went to America, he had asked Otto Bayer(17) for a meeting. The question of *why efforts were not made to keep Hans Muxfeldt in Germany or promptly to get him back* has never satisfactorily been answered. Not by Brockmann, not by Inhoffen, both of whom were convinced of Muxfeldt's scientific talents, and also not by Bayer, who had attempted to obstruct the migration of German scientists abroad through a "patriotic appeal".[71]

It is a nice academic tradition, when a colleague attains a certain venerability, to commemorate his or her achievements in a Festkolloquium. On Hans Herloff Inhoffen's 70th birthday in 1976 a gathering took place in Braunschweig. It was to be the last time in his institute, the fortunes of which Professor Inhoffen had decisively determined for three decades.

Five years later, another commemorative colloquium was held for Inhoffen, this time in Göttingen, at the Max-Planck-Institut für Biophysikalische Chemie.[18] Manfred Eigen had not only made the invitation, but also gave the main lecture,[19] on the attractive theme of *Goethe, Darwin and Molecular Biology*. With this initiative Eigen was commemorating efforts made jointly with Inhoffen since 1964 to establish the newly autonomous field of molecular biology in an interdisciplinary research institute in Germany north of the Main, where scientists from nearby universities and Max Planck institutes might carry out research under one roof. The high regard that Eigen showed for Inhoffen in his key lecture at the Festveranstaltung may really only be gauged by one aware of Eigen's constant refusal to accept C. P. Snow's demarcation line between the two cultures of the natural sciences and the humanities[85] and of the clarity of Eigen's answer to the poet's question of "*What, then, is life?*". Had the Göttingen scientist, who would be granted only partial recognition by description as merely a chemist, physicist or biologist, observed in Thomas Mann[86] that the novelist, for his chapter *Forschungen* in the *Zauberberg*, had not only excerpted, but also in a way reformulated Oskar Hertwig's *Allgemeine Biologie*[87] as if he knew more here than Hertwig's text knew and Thomas Mann could thus know.[85]

In Johann Wolfgang von Goethe we have a case far surpassing the literary genius and acute intellect attributed to Thomas Mann. Goethe, in the company of Herder and Schelling, adopted a posture opposing the mechanical world-view of Descartes and Newton. For him, nature was no product of a designer. Nature was self-reproductive and developing, and so could have a history. In this epoch of German Romantics with the romantic conception of life, Goethe was a forerunner of Darwin.[88]

The registration of the previously mentioned *Gesellschaft für Biotechnologische Forschung (GBF)*[20] in the Braunschweiger Handelsregister in May 1976 would certainly not have come to pass without its two primary instigators Eigen and Inhoffen, who functioned in tandem from the outset, like a well adjusted machine. They practiced an effective division of labour, Inhoffen canvassing leading figures in politics, business and public life for interest and active support, while Eigen proposed the scientific framework within which research in molecular biology should operate. The beginning of these collaborative efforts was dictated by chance: at the end of 1964 a newly completed industrial complex on the outskirts of Braunschweig was offered for sale as the result of a takeover. In 1965 it was bought by the *Stiftung Volkswagenwerk* at the urging of Professor Heinrich Nordhoff and was later to provide the foundation for what was to be the GBF. In accomplishing their plans, Inhoffen and Eigen also saw a welcome opportunity to escape some marked constrictions. On one hand there was a spatial constriction, which hampered or even prohibited the installation of large pieces of equipment, and to this was added a financial constriction, which no longer permitted the operation's running costs to be met from the Braunschweig institute's budget. On the other hand, there was also the petty attitude of the university towards doctoral study and habilitation in the Göttingen Max Planck institutes. The last difficulty was of fundamental importance: the new institute in Braunschweig should enable young scientists to build their own research groups and profiles for future careers. As well as this, it was possible to begin immediately with lectures for large audiences in the field of molecular biology, without requiring the approval of the Universitätsgremien, which was entrusted with old *Fächerkanon*. In 2001, the Gesellschaft für Biotechnologische Forschung, which had begun in 1965 through the initiative of Inhoffen and Eigen as the *Institut für Molekulare Biologie, Biochemie und Biophysik*, was transformed into the *Helmholtz-Zentrum für Infektionsforschung*. What in retrospect has proven to be a great leap[89] was not always seen as a step in the right direction during the walk.[90]

The *Braunschweiger Zeitung* of 27. February 2003 reported that a road to the GBF site was to be renamed Inhoffenstrasse. According to this report, the decision by the city council had been made after some emotional debate. The grounds for this were Inhoffen's brief membership of the SA (the Nazi Brownshirts) from 1933−1935. The *Entnazifizierungshauptausschu*β (denazification committee) of the city of Braunschweig had ruled in 1949 that Inhoffen had not been a member of the NSDAP (*Nationalsozialistische Deutsche Arbeiterpartei* − the actual Nazi party), but had belonged to the SA for two years as an ordinary member. This official report offers an answer to the question posed by Carl Djerassi in his 2001 book *This Man's Pill (Reflections on the 50th Birthday of the Pill)*[21].

Djerassi received the Inhoffen medal in Braunschweig in 1999. The name of Hans Herloff Inhoffen had been familiar to him since his dissertation. In the intervening period Djerassi's interest had shifted from Inhoffen's science to the man. In particular he wanted to know: *Had he been a Nazi?* In response to some inquiries, he received a letter from, as the letter's recipient comments, "one of Germany's most distinguished contemporary chemistry professors". From this letter from that anonymous colleague, Djerassi quotes, "*I would say that Inhoffen was what in this country is known as 'ein kleiner Nazi.' He certainly was not an anti-Semite... His eternal problem − in practically all fields − was that he never was first...*"

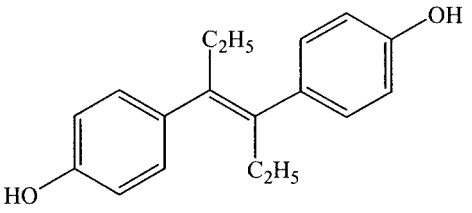
Now, this information about Inhoffen asks for some comment. Formally, for someone who had for two years belonged to the SA to be called a "kleiner Nazi" is hardly something to complain about. Inhoffen would later (after 1945) occasionally talk about what moved to join the SA in 1933, and it appears consistent with what Nicolaus Sombart has described as the "*men's club syndrome*" *as a factor in German national history from the end of the 19th century*[22].[92] What motivated Inhoffen to leave the SA in 1935 is unknown. Peter Inhoffen's (born 1934) *Erinnerung an kleine Erlebnisse eines Kindes im Dritten Reich*[23] [93] does not help any further here, apparently only recommending that account should be taken of characteristic behaviour as well as formalities. In addition, it should not be overlooked that to leave the SA in 1935 was much less normal than to join it in 1933.

During the *Third Reich* Inhoffen had the good fortune at any given time to be working in a scientific environment, characterized to a greater or lesser degree by open rejection of National Socialism. Windaus made no secret of his attitude, refusing to sign a loyalty declaration to Hitler. When students and doctorands in his institute attempted to prevent a Jewish doctorand from completing a dissertation, Windaus sought backing from the *Reichserziehungsministerium* in Berlin, demanding early retirement otherwise. The ministry ensured that the troublemakers in the institute had to change university, that the Jewish student completed his doctorate, and that Windaus was able to continue his research.[94] Wilhelm Bartmann,[65b] after a thorough study of documents from the Schering Archive, obtained the impression that the Berlin pharmaceutical company, where Inhoffen was engaged as a chemist after his research with Sir Charles Dodds, attempted *to carry on its business as if the National Socialists did not exist* during Nazi rule. He mentions the later report of one person affected, who speaks of a medical-scientific group of Schering *where there were only anti-Nazis.*

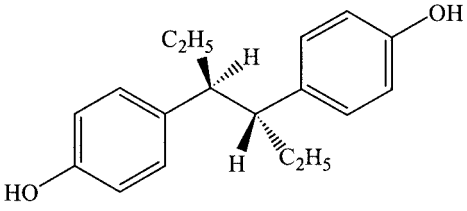
A reader who has attentively followed the above remarks is unlikely to accept that Inhoffen was "never first." Djerassi's source is simply not well enough informed. Why Djerassi nevertheless quotes him, although fully acknowledging Inhoffen's forerunner role in his scientific publications, remains his secret.

From R. B. Woodward's essay on the *Total Synthesis of Chlorophyll*[95] it may be inferred that Inhoffen, once he had let Hans Muxfeldt press on alone to the goal of tetracyclin synthesis, occupied himself with the fascination of chlorophyll chemistry. In any case, between 1964 and 1981 there appeared over 40 publications on investigations into porphyrins, chlorins or corrins. The habilitands H. Budzikiewicz, H. Wolf and H. Brockmann, jr., together with A. Gossauer and J. W. Buchler, were involved as co-authors.(24) The still outstanding great goals, such as the total synthesis of vitamin B_{12} or the elucidation of its biosynthesis, were not on the Braunschweig agenda and were solved elsewhere. Braunschweig contented itself with technically solid miniatures and was pleased to participate at all in this late activity vithin the field of natural products with low molecular mass.

In parallel with the studies on *Macrocycles with Four Unaltered or Reduced Pyrrole Rings*, between 1964 and 1973 there appeared experimental findings collected under the title *Studies on Highly Substituted Ethylenes and Glycols* and concerning pseudosteroids. *Pseudosteroids* here are partially or fully hydrogenated stilbene derivatives, which, although far removed from steroids in their constitutions, nevertheless display steroid-like biological activity. Sir Charles Dodds, Sir Robert Robinson and their colleagues had stumbled upon stilbestrol and hexestrol (Scheme 15) as molecules with high estrogenic activity in the mid-1930s. Thirty years later, Inhoffen set to work on these results obtained in the Courtauld Institute in London[96] and also used by Schering in Berlin,[97] looking for pseudosteroids that were biologically active without being estrogenic.



Diethylstilbestrol



Hexestrol

Scheme 15

The goal was not achieved; biological functions other than estrogenic activity effected by steroids appeared to be restricted to a rather narrow range of constitutions. In addition with increasing complexity of stilbene derivatives, caused by the presence of functional groups and stereogenic centres, asks more for the planning designer than for the improvising tinker.

This essay on Hans Herloff Inhoffen begins in 1931 with the completion of his dissertation under H. O. L. Fischer in Berlin and ends in 1981 with the celebration of his 75th birthday in Manfred Eigen's Max-Planck-Institut für Biophysikalische Chemie in Göttingen. The first 25 years and the final twelve are not commented on. In the former case, lack of source material would mean that speculation over beginnings was merely superfluous shooting into the undergrowth. In the latter case, there are indeed reliable letters in not unappreciable number; their tone, though, contrasts markedly with the earlier one. Clearly, the drastic diminution in his influence on further developments in Braunschweig made Inhoffen's reactions to supposed or actual disloyalty more aggressive and wounding. The existence of these letters is acknowledged, but they have not been evaluated. This may suffice to hint that mental and emotional plasticity were decreasing in his last years. It would give a false picture of Inhoffen's personality, though, if they were to have the last word.

Annotations

(1) Sterols (sterines) are readily crystallizable, high-melting alcohols structurally related to the tetracyclic choles-

terol. Other than the secondary alcohol group they contain no further functional groups (unless the C=C bond is regarded as a functional group). Molecules of this type possessing additional functional groups are classified as steroids, and so steroids are derivatives of sterols. Various subclasses are known: other than sterols, bile acids, sex hormones, glucocorticoids, mineralocorticoids, cardioactive glycosides, vitamin D compounds, and sapogenins.

(2) The fact that constitutional formulae containing quaternary carbon atoms belonging to three rings at once endured for so long, not even standing in the way of the award of Nobel prizes, has been commented on with amusement as misfortune[9] and more hostilely as a fiasco.[10]

(3) Unlike chemically based structural evidence, physically based structural evidence can be more clearly differentiated by yes-no questions. When he discarded the Windaus−Wieland constitutional formulae Bernal was using X-ray crystallographic analysis as a decisive source of information for the first time in the history of structural natural product chemistry.

(4) In order to ascertain the number of ring members present in carbocyclic rings of normal size, the cycloalkane ring is oxidatively opened to a dicarboxylic acid with the same number of C-atoms and the open-chain dicarboxylic acid is then heated with acetic anhydride. According to the Blanc rule[16] there would originally have been a five-membered ring present if the resulting product were a cyclic anhydride with a six-membered ring, or originally a six- or more-membered ring if the product were a cyclanone with one fewer ring member.

(5) There is not one single vitamin D and one provitamin D, but several. The molecules denoted with a 2 subscript have the C_9H_{17} side chain of ergosterol, those with a 3 subscript the C_8H_{17} side chain of cholesterol.

(6) 9α-Lumisterol is usually called pyrovitamin D_2, while 9β-ergosterol is generally known as isopyrovitamin D_2.

(7) On the term "spin isomer" see ref.[28a]

(8) J. D. Bernal had initially believed his X-ray structure analysis was only consistent with a tricyclic estrone.

(9) See ref.[44] for the concept and significance of Newman strain.

(10) In the second half of the 20th century a wish to integrate the previously separate fields[28b] of knowledge of natural products and understanding of chemical reactions developed in organic chemistry. This is made clear in the notable case of the isomerization of naturally occurring or synthetically produced cyclohexa-1,4-dien-3-ones to phenols.

(11) Prof. H. Hopf took over the management of the Institut für Organische Chemie at the Technische Universität Braunschweig as director in 1978, and in this function is the direct successor of Inhoffen.

(12) See ref.[63]: One day my colleague Walter Hohlweg, the physiologist who tested the sex hormones in animal experiments at Schering, came to me and said, "Could you make me a derivative of follicle hormone with the 17-carboxylic acid; I think it is effective for oral administration?" I gazed into space for a few seconds and said, "You can have the acid in two weeks. I'll add acetylene to estrone and then do an ozonolysis." The acetylenation was done in two days. Now it begins; Hohlweg examined every new hormone derivative prepared in the main laboratory for hormonal effects. I gave him around 50 mg of the new acetylene derivative, and then had to put aside the second step, the ozonolysis (for external reasons). Hohlweg then came to me after about two weeks, rushing in, and crying, "This acetylene derivative works very well as an estrogen, not just subcutaneously, but by mouth as well." The natural follicle hormone is practically ineffective orally. And with that was born the basic estrogenic material of what was to be The Pill. Had anyone known or wanted that before? Now there comes the end of the story. My colleague Professor Rudolf Wiechert at Schering later made Hohlweg's estradiol-17-carboxylic acid, clearly with some effort,[64] and it is completely inactive as an estrogen.

(13) After a brief *intermezzo* at the Universität Marburg, where Inhoffen was offered the directorship of the Physiologisch-chemisches Institut in the summer of 1946, and where he received the *venia legendi* for chemistry after giving his introductory lecture "On the History of the Discovery of the Antirickets Vitamins," he was called to the Ordinariat für Organische Chemie at the Technische Hochschule *Carolo Wilhelmina* in Braunschweig in the autumn of 1946. Two years later he took on a two-year stint in the office of rector of this, the oldest of the German Technische Hochschulen, which had suffered extensive damage from air-raids.

(14) Combinatorial Set of Virtual Synthesis Pathways for the Constitutionally Symmetrical Dimethylcrocetin.[28b]

(15) The greater part of financial contribution by the chemical industry to University teachers was administered in a performance-related and research-neutral fashion by the *Fonds der Chemie* (later the *Fonds der Chemischen Industrie*) through the so-called global distribution.

(16) In aldol condensations of this kind the later C_2-bridge between the ring A unit and the ring C component is supplied by the latter.[73,74] It can be produced through sequential addition steps from acetylene.[75] In a later version it is initialy situated on the ring A unit.[28d]

(17) Prof. Dr. Otto Bayer, Spiritus rector in the creation of the *Fonds der Chemie* and later its first speaker (1950−1964), made obstruction of the "migration of German scientists abroad" a matter of personal concern. On the 5th October 1951 the *Fonds der Chemie* made a *patriotic appeal* to University teachers. *It must be expected of every lecturer that he will* **...** *place his efforts solely in the service of the German Universities and Germany's reconstruction.*[71]

(18) Inhoffen and his wife had sold their magnificent house in Braunschweig in late 1979, moving to Göttingen.

(19) The central point of the lecture was the physical foundation for the Darwinian principle of natural selection; see ref.[84]

(20) The forerunners of the *GBF* were the Institut für Molekulare Biologie, Biochemie und Biophysik (IMB; **1965**) and the Gesellschaft für Molekularbiologische Forschung mbH (GMBF; **1968**).

[21] In the German translation based on the English original text the subtitle is "*Sex, Die Kunst und Unsterblichkeit*".

[22] See Nicolaus Sombart, *Männerbund und politische Kultur in Deutschland* in *Typisch deutsch: Die deutsche Jugendbewegung* (J. H. Knoll, J. H. Schoeps, Eds.), Opladen, **1988**.

[23] H. H Inhoffen's son, Emer. Professor in moral theology, University of Graz.

[24] The first three had come to Braunschweig after postdoctoral study with C. Djerassi at Stanford, to play a part in establishing the Institut für Molekulare Biologie, Biochemie und Biophysik.

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