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# Benzylisoquinoline Alkaloids from the Papaveraceae: The Heritage of Johannes Gadamer (1867−1928)

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Supporting Information

**ABSTRACT:** The substance archive of the laboratory of Johannes Gadamer (1867−1928), Marburg, Germany, was analyzed thoroughly with modern instrumental methods, with the samples purified when necessary, and the authenticity of the samples confirmed by historical and analytical evidence. Eight formerly unknown alkaloids of the benzylisoquinoline type were identified in the archive originally isolated from *Corydalis cava* or *Fumaria vaillantii*. This finding underscores the importance of the work of Johannes Gadamer and his group in stimulating overall progress in natural product chemistry. Several alkaloids were isolated by the group long before they were officially reported.

## INTRODUCTION

When Sertürner isolated morphine in 1817, he set the ball rolling for the development of the discipline of natural product chemistry. In the years following, the number of isolated natural products increased rapidly. The development of organic chemistry, which was initiated by Wöhler in 1828, enabled the first compound structural elucidations. With morphine, Sertürner had isolated the first alkaloid and, as it turned out, the first member of the large group of benzylisoquinoline alkaloids. In the course of time, many alkaloids were discovered in various plants, but, with few exceptions, only the main alkaloids were described. Structural and stereochemical information was mostly out of reach due to a lack of suitable technology. One must keep in mind that the era of alchemy and spagyrics had lasted until the beginning of the 19th century.

In 1898, Ernst Schmidt asked his assistant Johannes Gadamer to investigate *Corydalis* alkaloids. Gadamer had recently acquired the "venia legendi" for his work on the components of the seeds of *Sinapis alba* L.[1] He accepted, and the topic immediately fired his imagination. After the first alkaloid, corydaline, had been isolated by Wackenroder from *Corydalis cava* Schweigg. & Kört. in 1826, interest in this species had subsided and was revived only by Dobbie and Lauder at the University of Wales at Bangor, and Freund and Josephi at the University of Berlin, 66 years later in 1892. At about the same time, Schmidt decided to investigate this plant of the temperate zone, known as "hollow corydale". Freund and Josephi had recently begun research on this plant due to the unsatisfactory description of its main constituent, corydaline. The existing literature had mentioned two or three unknown alkaloids that had remained uncharacterized. The investigations of Freund and Josephi led to the discovery of bulbocapnine (named after the old name *Bulbocapnus cavus* Bernh. for *Corydalis cava*), corybulbine, and corycavine.[2] Dobbie and Lauder added corytuberine as a fifth alkaloid found in *C. cava*.[3] Although the discovery of new alkaloids from *C. cava* seemed to proceed, the structures of the first five alkaloids were still unascertained. Dobbie and Lauder tried to elucidate the structure of corydaline, but failed.[4,5] It would take 30 more years and the talents of Johannes Gadamer to solve this problem.[6] From 1898 to his early death in 1928, Gadamer contributed to the discovery of new alkaloids from hollow corydale and their structure elucidation.[7] Collaboration with another expert in the field of *Corydalis* alkaloids, Ernst Späth from the University of Vienna, Austria, resulted in additional findings and insights. Gadamer and his co-workers found seven new alkaloids in *C. cava*, of which four had not been isolated from any other plant, and they elucidated seven alkaloid structures from this species (Table 1).

Gadamer investigated also other plants from the family Papaveraceae, such as *Fumaria vaillantii* Loisel. He and his Ph.D. supervisor, Ernst Schmidt, had concluded from their experience with other Papaveraceae that protopine was a lead alkaloid of this family.[1,8] In order to prove this hypothesis, Gadamer assigned his student Hans Walter Braun the task of analyzing the whole plant of *F. vaillantii*.[9] He found protopine in all parts of the plant studied, in an overall amount of more

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**Table 1. Official Dates of Discovery and Structure Elucidation for 20 Alkaloids from *Corydalis cava* Relating to the Work of J. Gadamer**

| alkaloid | first documentation | first isolation from *Corydalis cava* | structure elucidation |
|---|---|---|---|
| bulbocapnine | 1893 Freund; Josephi[10] (*Corydalis cava* L.) | 1893 Freund; Josephi[10] | 1911 Gadamer; Kuntze[11] |
| canadaline | 1974 Gleye; Ahond[12] (*Hydrastis canadensis* L.) | | 1974 Gleye; Ahond[12] |
| canadine | 1873 Hale[13] (*Hydrastis canadensis* L.) | 1926 Gadamer; Knörck[14] | 1910 Faltis[15] |
| capnoidine | 1933 Manske[16] (*Corydalis sempervirens* Pers.) | 1969 Manske[17] | 1933 Manske[16] |
| corybulbine | 1893 Freund; Josephi[10] (*Corydalis cava* L.) | 1893 Freund; Josephi[10] | 1925 Späth; Dobrowsky[18] |
| corycavamine | 1893 Freund; Josephi[10] (*Corydalis cava* L.) | 1893 Freund; Josephi[10] | 1922 Gadamer; v. Bruchhausen[19] |
| corycavidine | 1910 Gadamer[20] (*Corydalis cava* L.) | 1910 Gadamer[20] | 1925 v. Bruchhausen[21] |
| corydaline | 1826 Wackenroder[22] (*Corydalis cava* L.) | 1826 Wackenroder[22] | 1922 Gadamer; v. Bruchhausen[6] |
| corydine | 1902 Gadamer; Ziegenbein[23] (*Corydalis cava* L.) | 1902 Gadamer; Ziegenbein[23] | 1931 Späth; Berger[24] |
| corypalmine | 1923 Späth; Mosettig[25] (*Corydalis cava* L.) | 1923 Späth; Mosettig[25] | 1925 Späth; Mosettig[26] |
| corytuberine | 1893 Dobbie; Lauder[3] (*Corydalis cava* L.) | 1893 Dobbie; Lauder[3] | 1931 Späth; Berger[24] |
| glaucine | 1839 Probst[27] (*Glaucium luteum* L.) | 1911 Gadamer[28] | 1911 Gadamer[28] |
| isocorybulbine | 1902 Gadamer; Ziegenbein[23] (*Corydalis cava* L.) | 1902 Gadamer; Ziegenbein[23] | 1925 Späth; Dobrowsky[18] |
| isocorypalmine | 1927 Gadamer; Späth; Mosettig[29] (*Corydalis cava* L.) | 1927 Gadamer; Späth; Mosettig[29] | 1927 Gadamer; Späth; Mosettig[29] |
| nantenine | 1926 Takase[30] (*Nandina domestica* Thunb. ex Murray) | 1969 Manske[17] | 1927 Kitasato[31] |
| protopine | 1872 Hesse[32] (*Papaver somniferum* L.) | 1904 Gadamer; Haars[33] | 1916 Perkin Jr.[34] |
| scoulerine | 1936 Manske[35] (*Corydalis scouleri* Hooker) | 1969 Manske[17] | 1936 Manske[35] |
| stylopine | 1901 Schlotterbeck; Watkins[36] [*Stylophorum diphyllum* (Michx.) Nutt.] | 1959 Trabert; Schneidewind[37] | 1926 Gadamer; Diester[38] |
| tetrahydropalmatine | 1923 Späth; Mosettig[25] (*Corydalis cava* L.) | 1923 Späth; Mosettig[25] | 1923 Späth; Mosettig[25] |
| thalictricavine | 1953 Manske[39] (*Corydalis cava* L.) | 1953 Manske[39] | 1953 Manske[39] |

**Table 2. Official Dates of Discovery and Structure Elucidation for Three Alkaloids from *Fumaria vaillantii* Relating to the Work of J. Gadamer**

| alkaloid | first documentation | first isolation from *Fumaria vaillantii* | structure elucidation |
|---|---|---|---|
| parfumine | 1969 Israilov; Yunusov[40] (*Fumaria parviflora* Lam.) | 1981 Israilov; Alimova[41] | 1969 Israilov; Yunusov[40] |
| protopine | 1872 Hesse[32] (*Papaver somniferum* L.) | 1956 Platonova; Massegatov[42] | 1916 Perkin Jr.[34] |
| stylopine | 1901 Schlotterbeck; Watkins[36] [*Stylophorum diphyllum* (Michx.) Nutt.] | 1979 Radu; Tamas[43] | 1926 Gadamer; Diester[38] |

than 50% of the total alkaloids of *F. vaillantii*. (The total alkaloid content is only 0.07% of dried mass.) Braun described three other unknown alkaloids that he was not able to characterize. The investigation of Braun is the first one documented on the alkaloids of *F. vaillantii* (Table 2). Gadamer did not publish the results from *F. vaillantii* because he could not determine the constitution of the unknown alkaloids and probably also because scientific interest in this plant was slight. The research on this plant "officially" started with publications from the Russian group of Platonova et al. in 1956. Until now, there are about 39 papers on this species.

## METHODS IN GADAMER'S TIME

In the late 19th and early 20th century, instrumental analysis had just begun to develop.[44] A survey of publications and Ph.D. theses from Gadamer's group yields the following picture: The most modern methods were the combustion analysis after Pregl and optical rotation after Laurent. Qualitative analysis heavily relied on physicochemical characterization (melting point, crystalline habit, solubility in organic and inorganic solvents, acidity and basicity) and color reactions. The color reagents—some are still used today as spot reagents in TLC—allowed for differentiation of alkaloids and alkaloid groups (e.g., Mandelin, Froehde, Erdmann, concentrated sulfuric acid, and concentrated nitric acid). Together with optical rotation and combustion analysis, these data provided much of what led to a first characterization of unknown substances. Gadamer collected (physico)chemical property sets that were common to alkaloids with the same skeleton and developed specific chemical reactions to distinguish the alkaloids. For example, oxidation with mercuric acetate was used to specify the quantitative amount of oxidizable methylene groups. Other reactions cracked up the molecule, and the formed fragments could be analyzed (again physicochemically and organoleptically), or functional groups were identified. From this information, the constitutions of compounds were determined as they were puzzled together.

The use of chromatography for the separation of natural product mixtures was instituted in the 1930s, too late for Gadamer's research. Before the development of chromatography the isolation of single compounds was laborious and tiresome, as exemplified by Gadamer's approach: The first step was an alcoholic extraction with hot or cold ethanol in a Soxhlet extractor (percolation) or via maceration, mostly conducted for several weeks until Dragendorff's reagent had turned negative (indicating no further extraction of alkaloids). The natural fats, resins, and chlorophyll were separated by filtration after addition of dilute acetic acid. All alkaloids were liberated and taken up in diethyl ether and chloroform by addition of ammonia to the acidic aqueous and alcoholic mixture. Evaporation of the organic solvents resulted in raw crystalline (diethyl ether) and amorphous (chloroform) extracts that were subjected to fractionation. First, the alkaloids were redissolved in diethyl ether and repeatedly shaken with definite portions of dilute hydrochloric acid. In this manner, fractions of different alkaloid salts were formed. Since cocrystallization occurred and many alkaloids had similar basic strength, another separation was achieved by fractionated crystallization from an appropriate


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**Figure 1.** Box containing C. Wachsmuth's compounds as found in the archive and sample of Haars "Base F 230 °C", later identified to be capnoidine.

nonpolar solvent for which the polarity was increased slowly with a polar solvent. From time to time, crystals were filtered off and the procedure extended until no more crystallization occurred. The last step of this time-consuming purification process was a recrystallization from a solvent that yielded ideally sizable crystals. For complete structure elucidation, amounts of pure substances in the range of one gram were needed. Consequently, some alkaloids could not be fully characterized. Nevertheless, there are exceptions to the rule: Isocorypalmine and scoulerine were identified by chemical reactions with amounts of only 10 and 100 mg, respectively.[29] These examples highlight that a synthetic approach was needed as final proof of a proposed structure. When structures were too complex for synthesis, further evidence was collected and relationships to other structures were determined. One example from Gadamer's substance collection is corycavine (corycavamine). Gadamer saw the similarity of this alkaloid to protopine but had no conclusive proof for its constitution.[45] When in 1916 Perkin Jr. came up with the unusual but undeniable structural evidence of a dibenz[*d*,*h*]azecine skeleton for protopine, Gadamer challenged the findings but soon realized that all evidence from his own research was in agreement with the proposed structure.[1] His Ph.D. student F. von Bruchhausen finally proved the structures of corycavine and another protopine alkaloid, corycavidine.[21]

## GADAMER'S HERITAGE REVISITED

After Gadamer's premature death in 1928, his Ph.D. students left Marburg, and the *Corydalis* alkaloids together with much of his scientific heritage from 30 years of research were stored in the Marburg Pharmacy Department and buried in oblivion. Extracts, pure and impure compounds, and semisynthetic derivatives from structure elucidation experiments were deposited in cigar cases before and after Gadamer's death. The cases had been numbered, with most bearing the name of the Ph.D. student or co-worker who had produced the materials contained therein. It cannot be reconstructed when and by whom these cases and the glass vials inside were labeled. The handwriting styles—in various hands, but all of them in an outdated German writing style called Sütterlin—point to the time when Gadamer was still alive or shortly afterward. By their labels the samples could be allotted to individual publications of Gadamer and the Ph.D. theses of F. Kuntze, F. v. Bruchhausen, C. Wachsmuth, K. Knörck, D. Bruns, H. W. Braun, and O. Haars. The labels on the samples prove that the collection had been moved from Marburg to Breslau and back, in accordance with Gadamer's academic career. The present Department of Pharmaceutical Chemistry, Philipps-Universität Marburg, Germany, graciously allowed us to take stock of and analyze the compound collection that had been stored in a room housing the departmental collections inclusive of Gadamer's work.

## ANALYSIS OF THE GADAMER COLLECTION

The historical collection was analyzed by GC-MS, HPTLC, and UV, IR, and NMR spectroscopy. Further details are provided in an experimental section (see the Supporting Information).

Attention was focused on the benzylisoquinoline alkaloids isolated from *C. cava* and *F. vaillantii*. A total of 250 samples distributed over 11 separate boxes had to be analyzed. The initial screening was performed with HPTLC, UV, and GC-MS. Interesting samples were then fully characterized with NMR spectroscopy and optionally IR spectroscopy. In this manner, the validity of Gadamer's research on *Corydalis* alkaloids was confirmed. The quality of the samples exceeded all expectations. After a minimum of 80 years of storage, all alkaloids except the most unstable ones, e.g., corytuberine, had outlasted time almost unchanged, partly because they had been purified to the state of perfect crystals.

Samples labeled "Base F 230 °C" (Figure 1) and "Base F 137.5 °C" were assigned to the work of O. Haars (1905), who used exactly these labels in his Ph.D. thesis.[33,46] These two samples correspond to capnoidine and nantenine. Thus, Haars had isolated these alkaloids 65 years before Manske and 29 and 22 years before the first isolation from the eponymous plants. C. Wachsmuth had continued the work of O. Haars and contributed to the knowledge of the unknown substances by identifying all functional groups with chemical reactions.[47] Figure 1 shows the box with the compounds from Wachsmuth's thesis as preserved in the archive. One alkaloid he isolated was stylopine (also called "Wachsmuth'sche Base", "Wachsmuth's base"), which was elucidated two years later by Gadamer and Diester in 1926.[38] Wachsmuth had isolated stylopine from *C. cava* 35 years earlier than Trabert and Schneidewind. Another unknown alkaloid was thalictricavine (original label: "Base F 148 °C"), which he related to canadine. His inference was almost correct, as we found his sample indeed to be thalictricavine (13-methylcanadine). Again, this discovery was


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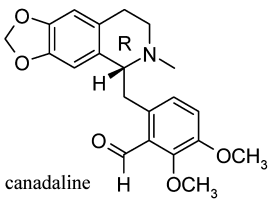
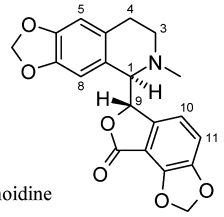
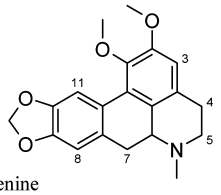
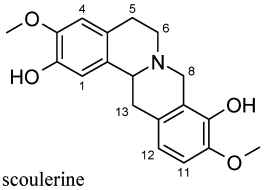
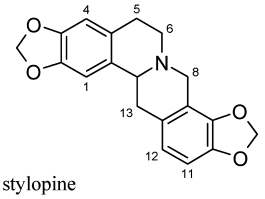
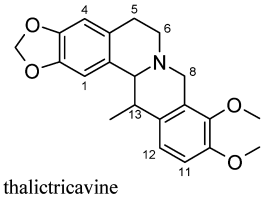
**Table 3. Corrected Discovery Dates for Six Alkaloids from *Corydalis cava***

| alkaloid | official discovery | actual discovery | structure elucidation |
|---|---|---|---|
|  canadaline | - | 1926 Knörck[14] | 1974 Gleye; Ahond[12] |
|  capnoidine | 1969 Manske[17] | 1904 Haars[33] | 1933 Manske[16] |
|  nantenine | 1969 Manske[17] | 1904 Haars[33] | 1927 Kitasato[31] |
|  scoulerine | 1969 Manske[17] | 1926 Knörck[14] | 1927 Späth; Gadamer; Mosettig[29] |
|  stylopine | 1959 Trabert; Schneidewind[37] | 1924 Wachsmuth[47] | 1926 Gadamer; Diester[38] |
|  thalictricavine | 1953 Manske[39] | 1924 Wachsmuth[47] | 1953 Manske[39] |

29 years before Manske first published the isolation of the alkaloid from *C. cava*.

The substances from the Ph.D. thesis of F. Knörck from 1926 provided two unknown alkaloids, of which one was identified as scoulerine (original label: "HCl phenolbase"). This was structurally elucidated correctly one year later by Gadamer, Späth, and Mosettig.[29] Another sample was found to be canadaline (original label: "Base 121 °C"), a compound that was isolated from *Hydrastis canadensis* many years later in 1974.[12,14,29] This compound was found to be (−)-canadaline (*R*), the enantiomer of (+)-canadaline (*S*) from *H. canadensis*.[48]

Gadamer and Schmidt had surmised protopine to be a lead alkaloid found in plants of the Papaveraceae. In order to corroborate this, Gadamer asked H. W. Braun to isolate and identify the alkaloids from *F. vaillantii*.[9] Braun analyzed separately the roots, seeds, and aerial parts and found protopine to be the main alkaloid in all these parts of the plant. Whereas the roots contained protopine exclusively, Braun described three unknown alkaloids from the seeds and the aerial parts. Two of these alkaloids were well preserved in sufficient amounts. We identified them as parfumine and stylopine. Consequently, Braun had isolated parfumine 54 years and stylopine 52 years before their first published isolation. Parfumine was even isolated 42 years before its discovery in *Fumaria parviflora* by Israilov and Yunusov.[40] The remainder of Braun's third alkaloid was too small for structure elucidation.


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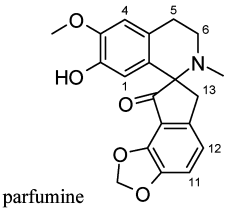
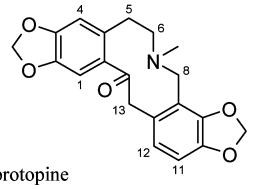
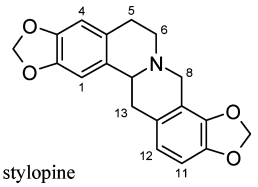
Table 4. Corrected Discovery Dates for Three Alkaloids from *Fumaria vaillantii*

| alkaloid | official discovery | actual discovery | structure elucidation |
|---|---|---|---|
|  parfumine | 1981 Israilov; Alimova[41] | 1927 Braun[9] | 1969 Israilov; Yunusov[40] |
|  protopine | 1956 Platonova; Massegatov[42] | 1927 Braun[9] | 1916 Perkin Jr.[34] |
|  stylopine | 1979 Radu; Tamas[43] | 1927 Braun[9] | 1926 Gadamer; Diester[38] |

## CONCLUSIONS

In summary, a reinvestigation and appraisal have been provided of Johannes Gadamer's work on benzylisoquinoline alkaloids. Tables 1−4 record the alkaloids found by our work and are placed in context with later isolation and structure elucidation work. An experimental section (Supporting Information) contains details of the present-day purification and characterization of the alkaloids isolated about 80 years ago. Interestingly, the part of the substance archive scrutinized by us contained one unknown alkaloid from *C. cava* [(−)-canadaline] and five alkaloids that were discovered 29 to 65 years before their official first isolation (Table 3). For *F. vaillantii*, Braun had extracted this plant very diligently and discovered a formerly unknown alkaloid (parfumine) and two unknown alkaloids for this plant (protopine, stylopine) (Table 4). All our findings have been supported and confirmed by analytical and historical evidence. We must pay respect to the precision and accuracy of the experimental work of Prof. Dr. Gadamer and his co-workers, which led to equally reliable and trustworthy publications. When Gadamer began his work on *C. cava*, five alkaloids, viz., corydaline, corybulbine, corycavine, corytuberine, and corydine, had been described superficially. From our survey of Gadamer's compound archive, we conclude his work added 15 alkaloids (Table 1). This number is impressive even though it represents 30 years of research, considering the methodology and technology available at the time. Gadamer and the scientists in his group achieved this with techniques that are vastly underdeveloped when compared with the situation today. However, the technical shortcomings spawned the progress of chemical science, especially in relation to our understanding of reactions and functional group properties. Today, we tend to underestimate the scientific skill and knowledge of natural product scientists in former times since we are spoiled by modern technological progress. This leads to the very imminent danger of loss of scientific knowledge and skill. For example, the patience and aptitude Gadamer and colleagues must have had with compound crystallization would help even today with the purification of natural products and other drug candidates.

## PERSPECTIVE

The majority of *Corydalis* alkaloids belong to the class of protoberberine and aporphine alkaloids, two groups of alkaloids that show interesting pharmacological effects in the CNS such as dopaminergic and serotonergic stimulation/inhibition. However, the structure−activity relationships that promote these effects are still unascertained. Some members of the protoberberines such as stepholidine have drawn attention to this group of alkaloids after promising preclinical data, and it is currently being investigated in a clinical trial against schizophenia.[49] The alkaloids found in the compound archive of Gadamer were used for pharmacological screenings against the dopamine receptors $D_1$ and $D_{2L}$, the monoamine oxidase isoenzymes MAO A and B, and the important biotransformation enzyme cytochrome P450. None of the *Corydalis* alkaloids inhibited MAO A or B. The inhibition of cytochrome P450 enzymes was screened with the most relevant human enzymes and revealed that most of the alkaloids were inhibitors of CYP2C19 and CYP3A4, with some inhibiting CYP1A2. Screening against dopamine receptors displayed an uneven picture for the *Corydalis* alkaloids, but indicated the strong influence of minor changes and positional shifts of functional groups. Hydroxy groups, for instance, were necessary for $D_{2L}$ antagonism, whereas alkoxy groups were correlated with $D_1$ antagonism.[50] In summary, benzylisoquinoline alkaloids may show various activities at several clinical relevant targets that have still not been investigated thoroughly but may offer potential for the future treatment of CNS disorders.[51]

## ASSOCIATED CONTENT

### Supporting Information

Detailed description of the analytical methods and material (HPTLC, UV, GC-MS, NMR) and analytical data of the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alkaloids identified. This information is available free of charge via the Internet at http://pubs.acs.org.

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