

## WHEN PIPERIDINE WAS A STRUCTURAL PROBLEM

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In 1850-51 August Hofmann in London published his newly developed method for degrading amines, which he was later to call exhaustive methylation, including mention of its potential use on alkaloids (1). Within a year in 1852 Auguste Cahours in Paris announced the isolation of a new liquid base, piperidine,  $C_5H_{11}N$ , from pepper (2). When organic structural theory was introduced in 1858, the constitution of piperidine became a problem which today seems to have been tailor-made for Hofmann's new procedure. While it now seems hard to believe that such a simple molecule could have offered difficulties, it was not until about 1881 that the structure of piperidine was established. Ironically, although it was Hofmann himself who eventually applied the exhaustive methylation procedure to piperidine, he was unable to interpret correctly the course of the reaction before Albert Ladenburg explained it in 1883. The probable reasons for this lapse as well as other curious aspects of the early chemistry of piperidine emerge from the literature, which is notable for the cautious approach taken to what was considered proof of structure.

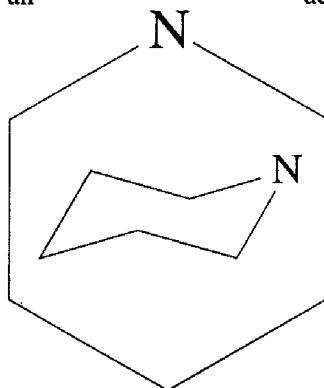
Piperidine became available early in the development of organic chemistry, at a time when few liquid organic bases were known, because it happened to be a component of the crystalline alkaloid piperine,  $C_{17}H_{19}NO_3$ , which had been isolated as early as 1820-21 from pepper (*Piper nigrum*) by Hans Christian Oersted in Copenhagen (3, 4), who suggested the name, and

by Joseph Pelletier in Paris (5). Since piperine occurs to the extent of 5-10% in peppercorns from various sources (6, 7) and is easily extractable by alcohol, it was readily available to the chemical community across Europe. In fact, piperine became of theoretical interest in connection with early speculations on the nature of plant alkalis: Were they merely associations of ammonia with a carbon compound, or, as Liebig had suggested, did they belong to the class of amides [here meaning any organic radical attached to  $-NH_2$ ] (1a,8)?

In agreement with the latter view, Theodor Wertheim at Vienna in collaboration with Friedrich Rochleder at Lemberg found in 1845 that piperine

was split by aqueous alkali into an acid and a liquid base which they identified as aniline [known since 1826 (9)] solely on the basis of C,H and Pt analyses of the chloroplatinate (10). Later in 1849 Wertheim changed his mind (11) and decided that the liquid base fit better the properties of the isomeric picoline [now known to be  $\alpha$ ] recently discovered in 1846 (12, 13). Oddly enough, Wertheim made no mention of the boiling point of his base even though the reported atmospheric boiling points for aniline [ $182^\circ C$  (14)] and picoline [ $133^\circ C$  (12)] differed widely; he apparently had not determined this critical physical property!

It was the putative identification as picoline that led the French chemist Auguste Cahours to repeat Wertheim's isolation. Cahours wished to make a comparison of picoline with aniline, perhaps with the aim of determining the basis for their isomerism. Distilla-





Auguste-Thomas Cahours 1813-1891

tion of a mixture of piperine, water, and potassium/calcium hydroxide, followed by addition of more potassium hydroxide to the distillate, caused the separation of an oily base which Cahours distilled twice to obtain a colorless basic liquid of strong ammoniacal odor and constant boiling point  $106^{\circ}\text{C}$  (15). Although he did not say so, it was presumably this boiling point, much lower than that of either aniline or picoline, which first indicated to Cahours that he actually had a different base; he named the new compound piperidine because of its source (16).

Analysis of the free base and eleven of its crystalline derivatives fixed the formula as  $\text{C}_5\text{H}_{11}\text{N}$  [in Cahours' terms  $\text{C}^{10}\text{H}^{11}\text{Az}$ ] which was confirmed by two vapor density determinations, altogether a very thorough piece of work for the time (15). Cahours made no mention of the fact that his analysis of the chloroplatinate of the base from piperine differed appreciably from Wertheim's analysis of [presumably] the same derivative, but he did state that piperidine differs completely in composition and properties from picoline with which Wertheim had confused it (17). It is surprising to the modern reader that no melting points are reported in either Cahours' or Wertheim's papers; melting points had not yet come into general use as criteria of identity or purity (18). Relying on Hofmann's work on amines, Cahours concluded that piperidine was an imide base [= secondary amine] since it formed *mono*-methyl, ethyl, and [iso]amyl de-

rivatives. He further surmised that the two alkyl groups attached to the nitrogen atom might be ethyl and allyl. Beyond this in 1853 there was not much more that could be done in investigating piperidine.

Hofmann at this time was the Professor of Chemistry at the new Royal College of Chemistry in London. Cahours and Hofmann were already known to each other from having corresponded regularly about chemical matters of common interest (19). On a visit to Paris in 1850 Hofmann took the opportunity to become personally acquainted with Cahours (19); the two chemists hit it off well and became good friends. When Cahours visited London for several weeks in 1855 to learn about the state of chemistry there, he stayed with Hofmann, and they began joint investigations which resulted in publications on two topics, neither of which involved nitrogen chemistry (19, 20). They must have discussed piperidine during their time together in London or else in letters, but it was too early for collaboration on a *structure* for this alkaloid fragment. However, after the structural theory of 1858 had been introduced, the question of the structure of the simple piperidine molecule must surely have entered both their minds. Rather puzzlingly, Cahours never published on piperidine again, even though he did work on the structure of nicotine in 1879-83. Nor did Hofmann take up the problem until much later. Cyclic structures were unknown at this time, and perhaps Cahours and Hofmann, considering only acyclic arrangements, regarded the question of which simple alkyl groups were attached to the secondary nitrogen atom as being relatively unimportant.

During the period from 1857 to 1878 several chemists worked on piperine, but they were more interested in the non-basic part from its hydrolytic cleavage (21). Wertheim continued studying piperidine, and in 1863 he investigated the nitrosation reaction and its reversal but got no further before his early death in 1864 (22). In 1871 Karl Kraut in Hannover made several salts from the adduct of piperidine and chloroacetic acid but did not comment on the structure of the base (23). Eventually some evidence of interest on Hofmann's part came from a paper appearing in 1871, the first paper of the twenty-one-year old graduate student Julius Brühl, published from Hofmann's Berlin laboratory (24). In it Brühl pointed out that the constitution of piperidine was still not known, and he prepared some salts in the hope of transforming piperidine into a member of a known group of compounds, but without success. By now a cyclic structure was beginning to be considered because Brühl remarked on the likelihood that piperidine was formed from the entry of a bivalent  $\text{C}_5\text{H}_{10}$  group into

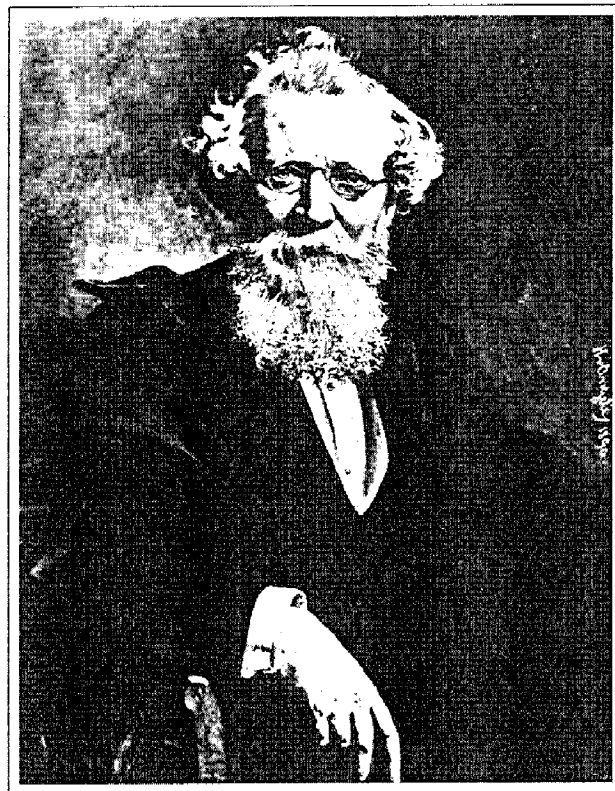
ammonia (25). Finally in 1879, Hofmann published his first work on the structure of piperidine (26).

Although by 1870 five- and six-membered rings were becoming generally accepted [e.g. benzene (1865), pyridine (1869-70), pyrrole (1870)], Hofmann pointed out that current chemical thinking still supposed that piperidine  $C_5H_{10}NH$  contained two alkyl groups, one being unsaturated, such as ethyl and allyl or methyl and crotonyl, a view unchanged since Cahours' statement in 1853 (15). He did not employ his exhaustive methylation method at first but instead tried to remove one of the [supposed] alkyl groups by the well-known procedure of heating with the strongest hydrochloric acid for days in a sealed tube, even up to  $300^\circ C$ , but no alkyl halide was split off (26). Nor did dry distillation of the hydrochloride salt give an alkyl halide. Reaction of piperidine with bromine in a sealed tube at  $200\text{--}220^\circ C$  afforded a crystalline product of dehydrogenation,  $C_5H_3NOBr_2$ , soluble in hot hydrochloric acid and in sodium hydroxide solution, which Hofmann was tempted to consider a pyridine derivative. However, because he was unable to obtain the same crystalline product from the reaction of bromine with pyridine [instead a dibromopyridine, m.p.  $109\text{--}110^\circ C$ , now known to be the 3,5-dibromo-isomer, was isolated], he did not insist on the crystalline product being a pyridine compound (26).

Hofmann was not the only chemist concerned with the structure of piperidine. Fortuitously in the same year, 1879, the young Wilhelm Koenigs at Munich announced in the *Berichte* that he had been able to oxidize piperidine directly to pyridine, albeit in low yield, with concentrated sulfuric acid at *ca.*  $300^\circ C$  (27). The pyridine was identified by odor and C,H and Pt analyses of its chloroplatinate salt. He felt confident that the formation of pyridine was structurally meaningful and not an artifact of cyclization, probably because he also found that ethylallylamine gave no trace of pyridine when heated with sulfuric acid (27). Therefore Koenigs proposed the reduced pyridine [*i.e.*, cyclic pentamethylenimine] structure for piperidine.

Almost two years later in 1881 Hofmann finally reported on the application of his exhaustive methylation method to piperidine, first in a preliminary notice (28) followed shortly by the full description (29). While the method had been announced 30 years previously (1), this was the first application to a compound of unknown structure. Hofmann was well aware of Koenigs' oxidation of piperidine to pyridine, but he was skeptical of the significance of the result because of the low yield and brutal conditions; he was still thinking in terms of a dialkylamine and was expecting removal of an alkyl

group when dimethylpiperidinium hydroxide was distilled. When he found by analysis that no alkyl group had been lost, and the product,  $C_7H_{15}N$ , named dimethylpiperidine by him, formally contained two methyl groups added to piperidine, he was puzzled by this apparent violation of his own rules for decomposition of quaternary ammonium salts: It was not possible to add two methyl groups to the secondary nitrogen atom of piperidine and still have a tertiary amine. As a way out of this quandary, Hofmann was initially inclined to think "dimethylpiperidine" might be a dimethylangelamine [angelyl =  $CH_3\text{--}CH=C(CH_3)\text{--}CH_2\text{--}$ ]. Although this idea was close to the truth, he rejected it on the basis of the following experiment: When the dry hydrochloride salt of "dimethylpiperidine" was heated, methyl chloride was evolved. The residue from this pyrolysis on treatment with alkali yielded a



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liquid base which he reported to have the same boiling point  $107^\circ C$  as the known monomethylpiperidine and to form the same crystalline chloroplatinate derivative as methylpiperidine. Hence, whatever the structure of the  $C_5$ -portion of piperidine might be, Hofmann believed [mistakenly as it turned out] it to be unchanged by the exhaustive methylation to "dimethylpiperidine."

Hofmann's solution to the problem was to suggest that during methylation the second methyl group introduced had become attached to a *carbon* atom of piperidine. In proposing this he was unfortunately misled by his own earlier work in which he and Ernst Mylius had found that trimethylanilinium iodide did undergo thermal change above 220°C to N,N-dimethyltoluidine [ortho from its b.p.], overall a true case of methyl moving from N to C (30).

After another methylation of the "dimethylpiperidine" and distillation of the quaternary hydroxide, Hofmann was again surprised to obtain trimethylamine and a liquid hydrocarbon C<sub>5</sub>H<sub>8</sub>, but he did not comment on the apparent return of the methyl group from carbon to nitrogen. The liquid hydrocarbon, b.p. 42°C, which he named piperylene, afforded a crystalline tetrabromide, m.p. 114.5°C. He considered several possible structures for piperylene, but a straight chain pentadiene was not one of them. In fairness to Hofmann, the two unexpected results forced him to reconsider what result to expect if piperidine actually did have the cyclic pentamethylenimine structure. He concluded that upon loss of trimethylamine, the carbon chain would reclose to give cyclopentene (31)! He realized that this was obviously not the case because cyclopentene, although not yet known, would give a dibromo derivative. At the end of this publication (29) Hofmann was left without a structure that would explain to his satisfaction all of the experimental results.

Even a year later, after Hofmann's co-worker Carl Schotten exhaustively methylated N-benzylpiperidine and obtained N,N-dimethylbenzylamine plus piperylene, *i.e.* the same outcome as with piperidine itself, the true course of the exhaustive methylation reaction still did not become apparent to them (32). Schotten was also able to convert piperidine directly to dibromopyridine by the action of bromine on dry piperidine hydrochloride at a much lower temperature (180°C) than for Koenigs' sulfuric acid reaction, but he did not comment on any possible significance of this observation for the cyclic structure of piperidine.

Hofmann continued work on the dehydrogenation and found that N-acetylpiperidine would react exothermically at room temperature with two molecular equivalents of bromine to form dibromopyridine [3,5-isomer], monobromopyridine [presumably the 3-isomer], and pyridine (33). Hofmann now accepted the cyclic six-ring structure for piperidine, but he still did not understand the exhaustive methylation results.

Finally in 1883 Albert Ladenburg, who had been working on the reaction of piperidine hydrochloride with methanol, had the insight to see clearly what had happened when dimethylpiperidinium hydroxide was heated: one of the ring bonds to nitrogen had been broken, and "dimethylpiperidine" was really CH<sub>2</sub>=CH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>. Further methylation and decomposition produced trimethylamine and piperylene which Ladenburg formulated as CH<sub>2</sub>=CH-CH<sub>2</sub>-CH=CH<sub>2</sub> (34). Much later it was found that piperylene was really the conjugated pentadiene CH<sub>2</sub>=CH-CH=CH-CH<sub>3</sub> (35), but Ladenburg had no reason to suspect this.

In the subsequent two years 1883-85 Ladenburg made further discoveries that removed any lingering doubts about the structure of piperidine. First he managed to isolate small amounts of piperidine from the sodium/ethanol reduction of pyridine (36) and later improved the procedure to give almost complete reduction of pyridine and better yields of piperidine (37). Finally, dry distillation of 1,5-pentamethylenediamine

dihydrochloride provided a direct synthesis of piperidine from a noncyclic precursor (38).

As noted earlier, Hofmann's major stumbling block to understanding the true course of the degradation of the quaternary hydroxide of piperidine was his conviction that the piperidine structure had survived this reaction unchanged. While he had considered the possibility that a cyclic piperidine might have been opened on heating the quaternary ammonium hydroxide, it did not occur to him that a ring might have been reclosed during the preparation and pyrolysis of the hydrochloride salt of "dimethylpiperidine" (29); Ladenburg did real-



Albert Ladenburg 1842-1911

ize this possibility. Only later in 1891 did Georg Merling carefully demonstrate that "dimethylpiperidine" did cyclize on treatment with hydrogen chloride, not to N-methylpiperidine, but to the isomeric N, $\alpha$ -dimethylpyrrolidine, b.p. 96–97°C (39). The two compounds can be distinguished by boiling point (10° difference) and by melting points of derivatives to which Hofmann's laboratory had evidently devoted insufficient care.

The problems in Hofmann's laboratory over the struggle to visualize the changes occurring during the stepwise exhaustive methylation of piperidine and the two-year lag before the correct explanation was forthcoming from another laboratory reveal in a striking manner the difficulty chemists had in adjusting their thinking to include the consequences of cyclic structures. A similar and even more difficult situation would be experienced somewhat later when three-dimensional cyclic structures were encountered in terpene and alkaloid investigations.

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