

The Contributions of A. W. Hofmann

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Atracurium and cisatracurium call attention to August Wilhelm von Hofmann (Figs. 1 and 2) (1). Actually, all of the neuromuscular blocking drugs should do so.

Hofmann (1818–1892) was the first chemist to synthesize quaternary amines (2,3). He wanted to convince chemists that so-called organic bases should be described, and conceptualized, as derivatives of ammonia. To that end, he converted ammonia into ethylamine and the then-novel compounds diethylamine, triethylamine, and tetraethylammonium (2–4).¹ The primary, secondary, and tertiary amines were stable during distillation at high temperatures under alkaline conditions. Interestingly, the quaternary amine was not. Heating quaternary tetraethylammonium hydroxide yielded tertiary triethylamine vapor. Thus was born the Hofmann elimination—a way to convert quaternary amines into tertiary amines (Fig. 3) (5,6).

Hofmann realized that his elimination reaction would prove a powerful tool for working out the molecular structures of the pharmacologically important alkaloids. The tool was ultimately applied to most of the alkaloid structures, including those of morphine, coca amine, atropine, and, interestingly, tubocurarine. Hofmann showed the way with coniine, the cholinergic poison of hemlock (7). Coniine is highly stable to heat and alkali. Hofmann used a methylating agent to quaternize coniine and to render it unstable. The Hofmann elimination then generated fragments that helped to piece the starting structure together (Fig. 4). Hofmann's coniine structure was the first structure of an alkaloid. Given a known structure by Hofmann, coniine became the first of the alkaloids to be artificially synthesized (8).

Parts of the tubocurarine molecule resemble coniine (Fig. 5), and these were revealed by methylation followed by Hofmann elimination, as in the case of coniine (9–12). Reporting a structure of tubocurarine in 1935, King (10) explicitly mentioned his application of “exhaustive methylation and degradation by Hofmann's method.” However, because of quantitative trouble with the methylation step of Hofmann's protocol, the 1935 structure erroneously carried an extra methyl group (13). Methylated curare (Metubine) was long called dimethyl-tubocurarine when it should have been called trimethyl-tubocurarine.

Tubocurarine is so chemically daunting that a revised structure took 35 yr to develop (13). Because of the mistakenly included methyl group, both of the nitrogens of tubocurarine were thought to be quaternary and to therefore each carry a fixed positive charge. Actually, one of the nitrogens of tubocurarine is tertiary, and that nitrogen is neutrally charged (when it is not reversibly protonated) (Fig. 5). Lacking a second fixed positive charge (and possessing other groups that can negatively ionize), tubocurarine penetrates into liver cells for significant hepatic elimination of its neuromuscular blockade (14). Until the structure of tubocurarine was revised, all synthetic curariform drugs were fully quaternary and relatively dependent on renal elimination.

Although fully quaternary, atracurium is not dependent on renal elimination. The drug can undergo Hofmann elimination. That oft-repeated phrase is a play on words. The word “elimination” has a pharmacological sense and a chemical sense. To Hofmann, “elimination” is a molecular fragmentation in which two parts of the molecule fall off and leave behind a double bond.

Unlike tubocurarine and morphine, atracurium undergoes Hofmann elimination at mild temperatures and pH values (1). The reason for its relative instability is that the ammonium group of atracurium is in the β -position with respect to a carbonyl group. Hofmann's sturdy reactants did not have this $-\text{CO}-\text{CH}-\text{C}-\text{N}^+$ feature. The carbonyl group weakens the $\text{C}-\text{H}$ bond of the α -hydrogen and thereby facilitates elimination of H^+ and tertiary amine from the quaternary

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¹ Hofmann coined much of the nomenclature of modern organic chemistry and pharmacology (3,4). He introduced the “-onium” suffix (and thus “-ium”) now applied, for instance, to rocuronium and atracurium. He also introduced the “-ane” suffix of cyclopropane and subsequent inhaled anesthetics.

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Figure 1. Hofmann during his tenure (1845–1865) as the first director of the Royal College of Chemistry, London.



Figure 2. Hofmann in his Berlin laboratory in 1870.

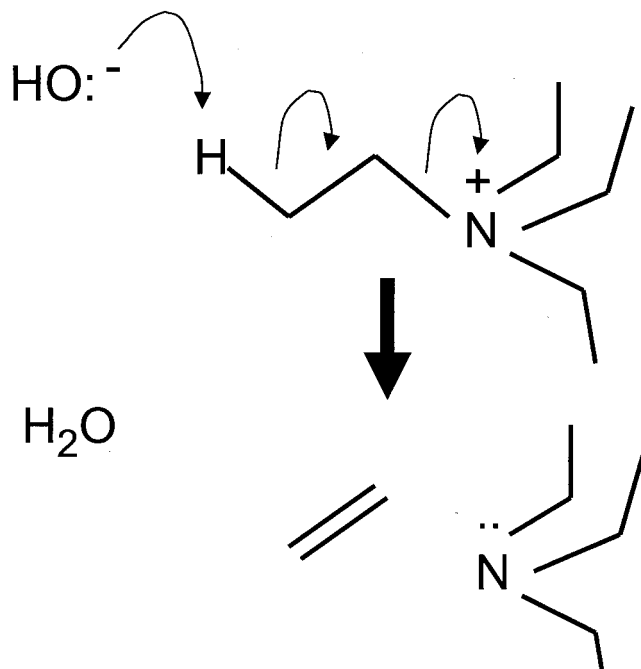


Figure 3. The Hofmann elimination of tetraethylammonium hydroxide.

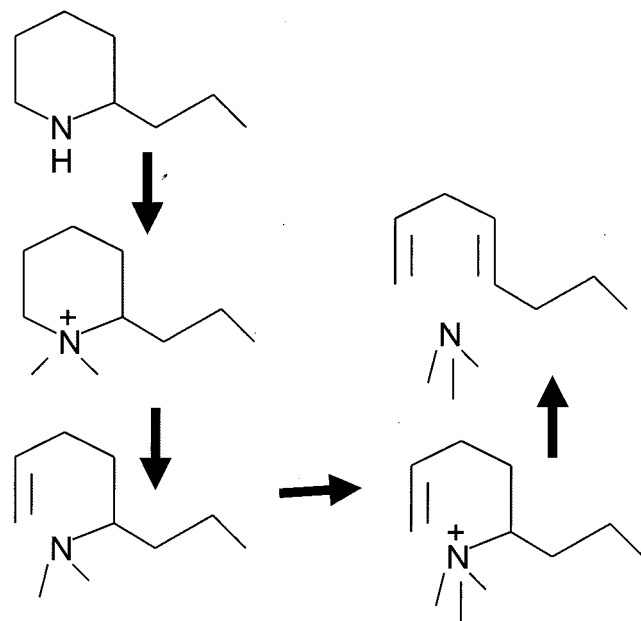


Figure 4. The “Hofmann degradation” of coniine. 1) A methylating agent converts the secondary amine to a less-stable quaternary amine. 2) A specific C—N bond is broken by heating under alkaline conditions (“Hofmann elimination”). 3) The product is methylated again. 4) The other C—N bond is broken (“second-stage Hofmann elimination”). The first C—N bond to break is reliably predictable (“Hofmann’s rule”). Note that the methyl group cannot undergo Hofmann elimination. Much structural information is gleaned by the often-used strategy. For instance, the sequence identifies the starting alkaloid as primary, secondary, or tertiary. Also, the cyclic or noncyclic nature of the amine is revealed. The discrete fragments become pieces of a puzzle.

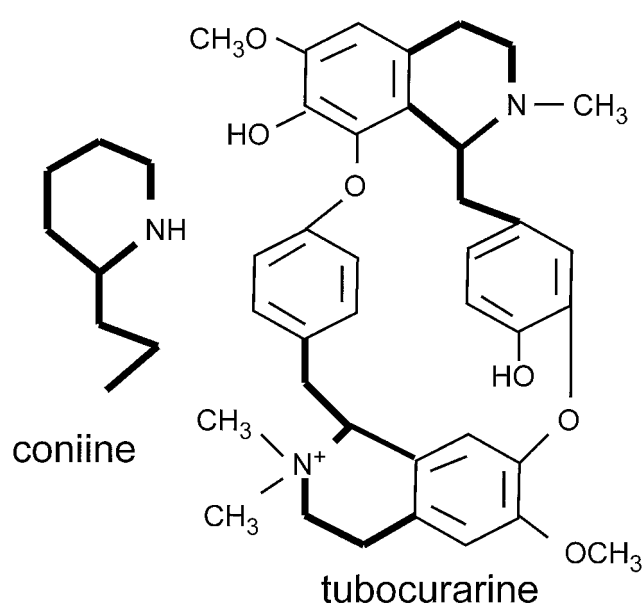


Figure 5. Structural diagrams of coniine and tubocurarine. Two coniine-like parts are apparent in the larger molecule.

amine. Facile eliminations adjacent to carbonyl groups are usually called " β -eliminations" or "Michael eliminations" (after an American who had studied under Hofmann) (15,16). Mechanistically, it would be more informative to call the atracurium decomposition a " β -elimination" (rather than a Hofmann elimination), indicating that the elimination is facilitated by a suitably positioned carbonyl group. All of the muscle relaxants can undergo Hofmann elimination under the harsh conditions of Hofmann. Only the atracurium isomers can undergo β -elimination. Although the name of Hofmann does not explain the instability of atracurium, it does provide information. Hearing of Hofmann, the listener knows that atracurium is a quaternary amine that decomposes into a tertiary amine fragment and a fragment carrying a carbon-carbon double bond.

Atracurium instability is a strong function of pH. Because of the "electron-withdrawing" carbonyl group, the hydrogen to be eliminated is weakly attached to its carbon and is readily "pulled off" by the hydroxide ion at mild temperatures (1,16). Increasing the ambient pH from 3.4 to 7.4 increases the hydroxide concentration by a factor of 10,000 and commensurately accelerates the elimination reaction.

The Hofmann elimination is not the only Hofmann reaction in pharmacology. In addition to breaking down amines, Hofmann found clever ways to create amines. For instance, the "Hofmann rearrangement" changes a carboxylic acid into an amine (17), and his reactions remain powerful tools for the synthesis of pharmacological amines today.

His effect on pharmacology has been indirect but substantial. For instance, Hofmann influenced Alfred

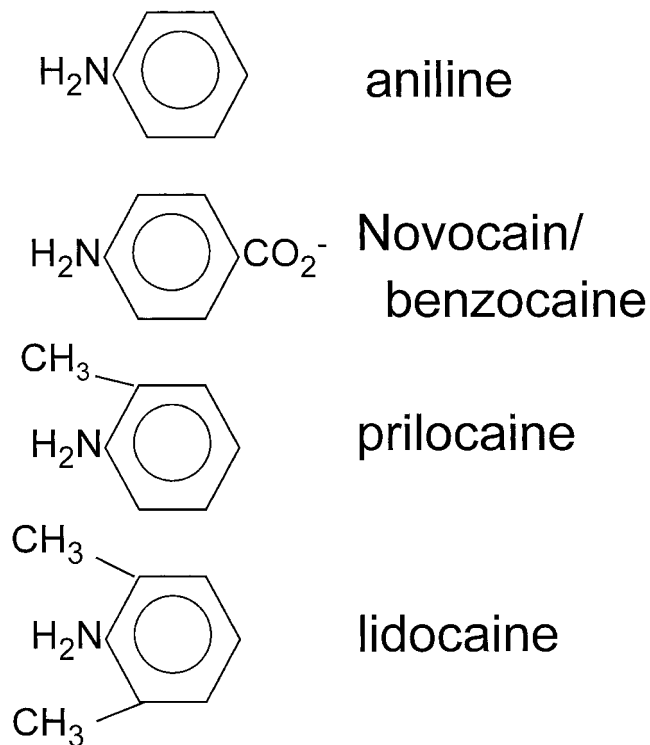


Figure 6. Structural diagrams of aniline and the aniline metabolites of selected local anesthetics. In his dissertation work, Hofmann found coal tar to be an inexpensive source of aniline, a molecule he called his "first love." He hoped to synthesize artificial alkaloids from coal tar. He failed to so obtain artificial quinine, and he did not live to see Einhorn prepare novocaine. However, he did explain why the lidocaine metabolite is relatively unable to oxidize hemoglobin. Two methyl groups effectively shield the amino group in the lidocaine aniline. The single methyl group of prilocaine is not an effective umbrella. Hofmann would surely be pleased to see the plethora of aniline-based drugs of the 20th century.

Einhorn, who gave us novocaine. Hofmann started out in chemistry by finding aniline in coal tar (Fig. 6). He wondered whether coal tar amines could be used to synthesize quinine, a precious antimalarial alkaloid that was in great shortage. Attempting to do so, William H. Perkin, a student of Hofmann, serendipitously synthesized the first aniline dye. That dye, mauve, was "a color that changed the world" (18). Perkin and Hofmann artificially created a series of spectacular textile dyes that replaced drab, expensive biological products. The fashion world contracted "mauve measles," and chemistry burgeoned with bright would-be entrepreneurs (19). With that history in mind, Einhorn naturally turned to aniline derivatives to come up with novocaine, a good local anesthetic that did not have to come from tropical plants (Fig. 6). Another aniline, fentanyl, was eventually prepared as an artificial analog of botanical morphine. Midazolam is also, structurally, a substituted aniline. More directly, an aniline dye provided the sulfa synthetic antibiotic miracle (20,21).

Aniline drugs are reactive chemicals and so have problems (19). For instance, benzocaine and prilocaine metabolites can oxidize hemoglobin. Two bulky methyl groups shield the amino group of the aniline-like metabolite of lidocaine, and the toxicity of lidocaine is thereby reduced (Fig. 6) (19). The decreased reactivity of dimethylaniline was the first example of "steric hindrance" in organic chemistry, and Hofmann was the discoverer of that safety feature of lidocaine (22).

Queen Victoria boosted obstetric anesthesia when she recruited John Snow to be the royal anesthetist. It is less appreciated that she greatly influenced anesthesia when she recruited 27-yr-old Hofmann to organize the Royal College of Chemistry.

The Hofmann images were provided by the University of Pennsylvania Library from their Edgar Fahs Smith Collection. The cited 19th-century articles were made available by the Countway Medical Library and the Conant Chemistry Library of Harvard University.

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