The purpose of this final article in the three-part series is to present the basics of balanced general anesthesia as developed during the past fifty years. These advances included syntheses of the benzodiazepines (sedative–hypnotics) and the amide opioids (analgesics); the first article (1a) in this series describes these two agents. Today it is common to employ a sedative–hypnotic, for example, midazolam, and an opioid analgesic, for example, fentanyl, as the sole medicants in a nonsurgical invasive procedure such as a colonoscopy. We note also that progress has been made in treating postoperative nausea and vomiting in the recovery room. As the narrative unfolds we will update developments in intravenous induction anesthetics and inhalational anesthetics (1b), so as to reflect current practices. A “visit” to a contemporary surgery will complete the story.

Preparation of Compounds

Rather than a barbiturate such as thiopental, 1, or methohexital, 2 (Figure 1), many anesthesiologists today are turning to propofol, 3 (Scheme I) as an induction anesthetic. Etomidate, 9, and ketamine, 15, are similar agents that find more limited use. The first commercial preparation of 3 (Scheme I) relied upon the direct Friedel–Crafts o,o’-bisalkylation of phenol. The pathway to 9, is longer, fabrication of the imidazole ring in intermediate 8 alone involving four separate reaction steps. N-alkylation of α-methylbenzylamine, 4, with ethyl chloroacetate, 5, in the presence of triethylamine leads to the N-substituted glycinate ester, 6. The N-formylation of 6 in refluxing formic acid followed by a mixed Claisen condensation \(-\text{NCH}_2\text{CO}_2\text{Et} \rightarrow -\text{NCH} (=\text{O})\text{CO}_2\text{Me}\) leads to the multifunctional compound 7. Ring closure occurs as 7 reacts with thiocyanic acid

![Scheme I. Syntheses of propofol, 3, etomidate, 9, and ketamine, 15.](image-url)
(HN=C=S) to form the methyl ester of 1-(α-methylbenzyl)-2-mercaptoimidazole-5-carboxylic acid, 8. Oxidative removal of the sulfur is followed by saponification, acid chloride formation, and a final reaction with ethanol to yield the ethyl ester known as etomidate, 9.

Assembly of the ketamine molecule 15 (Scheme I) begins with a Grignard reaction between 2-chlorobenzonitrile, 10, and cyclopentylmagnesium bromide, 11. Following α-bromination of ketone 12, liquid aminolysis is then used to transform bromoketone 13 into α-hydroxyimine 14. Water generated during imine formation apparently leads to hydrolysis of the adjacent C−Br bond. No rubric seems to exist to describe the thermal rearrangement of 14 into 15 (Figure 2). The accompanying diagram seems to be a reasonable pathway for what is almost surely a concerted reaction.

The inhalational anesthetic halothane, CF3CHBrCl, has been largely replaced by four polyhalogenated ethers: isoflurane, 19 (Scheme II) appeared in 1971 (5), to be followed by enflurane, 24 (6), and sevoflurane, 28 (7), in 1972, and desflurane, 29 (8), in 1988. Both steps in the synthesis of halothane (1b) from 1,1,1-trifluoroethane involved free radical halogenation. In Scheme II vapor phase free radical chlorination is the final step in the preparation of 19 and the next-to-last step in the syntheses of 24, 28, and 29. Otherwise the transformations are solution-based and the transformations are solution-based and the species are implicated. Two of the ether forming reactions, 16 → 18 and 25 → 26, are S_N2 in nature; the third, 21 → 22, proceeds via addition of the methoxide nucleophile to the electron-deficient carbon carbon double bond in 1-chloro-1,2,2-trifluoroethene, 21. Direct transformation of C−H to C−F is generally to be avoided; among the concerns is that elemental fluorine is a strong oxidizing agent. In the chemistry at hand it is a matter of transforming sp^3 C−Cl into sp^3 C−F. The routes various workers chose include the venerable Swarts reaction, 23 → 24 (enflurane), nucleophilic displacement by the fluoride anion under severe conditions, 27 → 28 (sevoflurane), and extended exposure to bromine trifluoride, 19 → 29 (desflurane).

Gram quantities of the two enantiomers, 34 and 35, optical purities > 99% enantiomeric excess, of isoflurane were prepared in 1993 (9). The initial reaction of Scheme III requires the transformation of 1,1,1-trifluoroethanol, 16, into an ether; product 30 has a pendant carboxylic acid group that allows for the later resolution of a racemic mixture. Free radical chlorination of an intermediate acid chloride gives the monochlorinated acid chloride 31 and the dichlorinated acid chloride 32. Ester formation with isopropyl alcohol is followed by chemoselective reduction of the ester of 32 to the ester of 31, with subsequent acid-catalyzed hydrolysis setting the stage for salt formation between racemic 33 and 34.

![Figure 2. The thermal rearrangement of 14 into 15.](image-url)
Scheme IV. Synthesis of atracurium besylate, 40.

Scheme V. Synthesis of rocuronium (bromide), 48.
(+)-dehydroabietylamine. Great care was essential in the final decarboxylation of each diastereomeric salt; configuration at the asymmetric carbon atom in the emerging isoflurane enantiomer was maintained only when precisely one equivalent of potassium hydroxide was used. Comparison of 34 and 35 in mice showed that the (S)-(+) form was only marginally more potent (10).

The rudiments of balanced general anesthesia include a muscle relaxant. A number of compounds have been developed as successors to curare and succinylcholine dichloride (1b). We limit ourselves to two substances with quite dissimilar structural frameworks: atracurium besylate, 40 (Scheme IV) (11), and rocuronium, 48 (Scheme V) (12). The initial step in Scheme IV is simply the combination of unsaturated acid chloride 36 with 1,5-pentanediol, 37, to provide ester 38. The hetero-Michael addition of two equivalents of racemic tetrahydropapaverine, 39, to achiral 38 precedes the final quaternization of two tertiary nitrogen atoms with methyl benzenesulphonate. As produced commercially atracurium besylate, 40, is a mixture of ten stereoisomers. Two tetrahydrosoquinoline rings are present in compound 40 and in tubocurarine dichloride (curare) (vide infra) as well.

Rocuronium, 48 (Scheme V) is a steroid-based neuromuscular blocker that was designed so as to “incorporate acetylcholine-like fragments,” that is, MeCO2–C–C–NR 3. Proceeding from 5α-androst-2-ene-17-one, 41, acid-catalyzed acetylation of the enol tautomer via isopropenyl acetate generates diene 42. Bispoxidation of 42 with perbenzoic acid is stereoselective as both heterocyclic rings form preferentially from the rear (α) side. The transformation of intermediate 43 can be understood as both a chemo- and a stereoselective attack by the pyrrolidine nucleophile, 44, from the front (β) side of the five-membered carbocyclic ring, to generate monoepoxy ketone 45. Stereoselective reduction of 45 with sodium borohydride (hydroxide ion transfer occurring from the rear) is followed by a regioselective and stereoselective opening of the second epoxy ring with morpholine, 46. Both secondary alcohols in 47 react readily with acetyl chloride to generate acetate ester groups; a final reaction of the diester with allyl bromide provides the pure stereoisomer 48 in 70% yield after chromatography on alumina. One may presume that the less basic morpholino nitrogen does not react, even with the initial molar ratio of alkylating agent to substrate being eight to one.

**Correlation between Structure and Activity**

Whereas the earlier induction anesthetics thiopental, 1, methohexital, 2, and thiamylal were all barbituric acid derivatives with pK\textsubscript{a}’s around 8 (1b), the lone link between the newer agents, 3, 9, and 15, is the presence of a substituted benzene ring. The chemistry of propofol, 3, pK\textsubscript{a} 11.1, under physiological conditions is that of the neutral and highly lipophilic molecular form. An aqueous emulsion of this phenolic compound containing 1% propofol, 10% soybean oil, 2.2% glycerol, and 1.2% egg phosphate is injected intravenously. Penetration of molecular propofol across the blood–brain barrier is rapid, as is its subsequent redistribution to other sites, including the liver. Compared to thiopental the incidence of postoperative nausea and vomiting with propofol is significantly lower. The acid–base chemistry of etomidate, 9, entails protonation of the imidazole ring, A pK\textsubscript{a} of 4.1 (conjugate acid) ensures that etomidate is also borne along in the blood (pH of 7.4) as a neutral, highly lipophilic, molecule. Etomidate is vulnerable to enzymatic hydrolysis (and deactivation). Whereas propofol and etomidate interact with GABA\textsubscript{A} (gamma-aminobutyric acid) receptors in the brain, ketamine, 15, seeks out sites linked to NMDA (N-methyl-D-aspartic acid). Compared to 3 and 9 the proportion of the cationic form (pK\textsubscript{a} 7.5) of ketamine in the blood as well as in the aqueous cell environment is much greater; 15 is injected as an aqueous solution of the hydrochloride salt. Ketamine is an α-amino ketone with analgesic properties (cf. the amino esters and the α-aminoamides as local anesthetics; ref 1a). Propofol, etomidate, and ketamine all provide rapid induction, although preference is generally given to propofol. Etomidate is an excellent choice where compromised cardiovascular function exists, for this agent promotes homeostasis of the heart and the circulatory network. Ketamine finds occasional use as a pre-induction sedative in regional anesthesia involving young children and older adults.

Aware of the liver and kidney damage associated with chloroform anesthesia, hospital personnel were concerned that halothane, F3CCCHBrCl, might also prove to be hazardous. Although the majority of the anesthetic is ultimately expired by the patient, some 10% to 20% of the administered drug undergoes enzymatic metabolism in the liver. A single exposure to halothane carries only minimal danger of liver damage, but may foster the creation of antibodies. Additional exposure to halothane is deemed highly risky. Biotransformation of halothane occurs via oxidative deamination, mediated by cytochrome P450 enzymes (monoxygenases). Attack at the lone C–H bond leads to C–O–H, followed by loss of the geminal bromine:

\[
\text{F}_3\text{CC} - \text{C} - \text{Cl} + \text{H}^+ + \text{Br}^- \rightarrow \text{F}_3\text{CC} - \text{C} - \text{Br} + \text{H}_2\text{O}
\]

The replacement of the bromine in halothane by a difluoromethoxy group led in 1971 to a new anesthetic, isoflurane, 19, that was expected to be metabolically more stable.\textsuperscript{5} A year later it was joined by a constitutionally isomeric inhalant to be known as enflurane, 24, as well as a heptafluoroether that was named sevoflurane, 28. The extent of liver-based metabolism of each is greatly diminished relative to halothane and is understood in terms of a mechanism wherein oxidation is preceded by removal of the hydrogen atom to generate a free radical. The more electronegative the substituents are, the stronger the C–H bond energy is and the slower the rate of degradation. That only 1% of 19 undergoes metabolism is attributed to the replacement of the
bromine in halothane by the difluoromethoxy group. The degrees of biodegradation of 24 and 28 are minimal as well:

\[
\begin{align*}
&19 \quad \rightarrow \quad 49 \\
&24 \quad \rightarrow \quad F_2\text{CHOCF}_2\text{Cl} \\
&28 \quad \rightarrow \quad (\text{CF}_3)_2\text{CHOH}
\end{align*}
\]

Less that 0.1% of desflurane, 29, is metabolized, its low reactivity consistent with fluorine being the only halogen present. What little is degraded turns up as trifluoroacetyl chloride, 49.

Subsequent reaction of 49 or \( \text{F}_2\text{CHOFCF}_2\text{Cl} \) with endogenous protein leads to impaired cellular chemistry within the liver microsome and the appearance of neoantigens:

\[
\text{protein} \quad \rightarrow \quad \text{NH}_2 + 49 \quad \rightarrow \quad \text{CF}_3\text{CONH} \quad \rightarrow \quad \text{protein}
\]

Sevoflurane is the least problematic; not only is its degree of degradation minimal but each of the fragments, \((\text{CF}_3)_2\text{CHOH}, \text{CO}_2, \) and fluoride ion, are safely eliminated. Sevoflurane is degraded (13) during the rebreathing–recycling process to a substance that is a nephrotoxin (kidney) in rats; with low-flow anesthesia the anesthetic does not cause renal dysfunction (14):

\[
\text{H} - \text{F} - \text{CF}_3 \\
\text{FCH}_2\text{O} - \text{C} - \text{CF}_2 \quad \text{NaOH} \quad \text{HF} \quad \text{FCH}_2\text{O} - \text{C} = \text{CF}_2 \\
\]

Selection of an inhalant by an anesthetist is generally an individual decision. Variation between the agents as to rapidity of induction and recovery is modest. The vaporizers in anesthesia machines are normally designed to handle liquid agents with boiling points between 50 °C to 60 °C. Of the materials mentioned (including halothane as well), desflurane with a bp of 23.5 °C is the exception.

It was for acetylcholine chloride (\( \text{ACh} \)), 50, and \((\pm)\)-tubocurarine dichloride, 51, to serve as templates for the preparation of synthetic neuromuscular blocking agents (Figure 4). Researchers found example after example of compounds that were active at receptor sites; a critical element was the presence of one or more tetrakisalkylated ammonium ions, \( \text{R}_4\text{N}^+ \). Also \( \text{R}_4\text{N}^+ \) binds somewhat more strongly that does a trisalkylated ammonium ion, \( \text{R}_3\text{NH}^+ \). Tubocurarine, 51, is a drug of long (comparatively) duration and much of the drug is eliminated unchanged by the kidneys. As ester derivatives atracurium, 40, and rocuronium, 48, both undergo hydrolytic degradation in the plasma. In addition atracurium breaks down under physiological conditions by way of a Hofmann elimination reaction. These two agents are muscle relaxants of intermediate duration. The modes of action of 40 and 48 are analogous to that of 50; each is a competitive and nondepolarizing muscle relaxant (1b).

**Figure 4.** Compounds that served as templates for the preparation of synthetic neuromuscular blocking agents.

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**In the Classroom**

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**Notes**


3. The efficient transmittal of the information in the schemes and illustrations is facilitated with these abbreviations: Me = methyl, Et = ethyl, Pr = propyl, i-Pr = isopropyl, Ph = phenyl, Ac = acetyl, h = hour, aq = aqueous, and hν = light.

4. Intramolecular hydrogen bonding very likely plays a role; the changes in bonding are reminiscent of a Wagner–Meerwein rearrangement.

5. Homolytic bond energies decrease from C–F to C–Cl to C–Br. Thus the most reactive halogen is the one that was replaced in halothane in preparing isoflurane.

6. The device measures pulse rate and oxygen blood level.

7. Precordial indicates the sensor is placed over the heart at the bottom of the thorax.

8. A BIS sensor is placed on the forehead and then connected through a cable to a monitor. Brain activity is measured to provide a numerical indicator of the level of awareness. http://www.aspectmedical.com/patients/bis/default.mspx (accessed Aug 2006).

9. This local anesthetic (1a) is a prophylactic to reduce the localized discomfort of a propofol injection.

Literature Cited


