Chemical Aspects of General Anesthesia: 
Part II. Current Practices

Robert Brunsvold
Department of Anesthesiology, Meritcare, Fargo, ND 58123

Daryl L. Ostercamp*
Department of Chemistry, Concordia College, Moorhead, MN 56562; *ostercam@cord.edu

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, midalozam, 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)\(^3\) (2), as an induction anesthetic. Etomidate, 9 (3), and ketamine, 15 (4), 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 \(\alpha\)-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 \([–\text{NCH}_2\text{CO}_2\text{Et} → –\text{NCH} (\text{CH} = \text{O})\text{CO}_2\text{Me}]\) leads to the multifunctional compound 7. Ring closure occurs as 7 reacts with thiocyanic acid.

Figure 1. Structure of two barbiturates.

Scheme I. Syntheses of propofol, 3, etomidate, 9, and ketamine, 15.
(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.

Assembly of the ketamine molecule (Scheme I) begins with a Grignard reaction between 2-chlorobenzonitrile, 9, and cyclopentylmagnesium bromide, 11. Following α-bromination of ketone 12, liquid methylamine 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 concerted4 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 charged species are implicated. Two of the ether forming reactions, 16 → 18 and 25 → 26, are SN2 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 sp3 C–Cl into sp3 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 chemo- or stereoselective 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

![Figure 2. The thermal rearrangement of 14 into 15.](image-url)

Scheme II. Syntheses of isoflurane, 19, enflurane, 24, sevoflurane, 28, and desflurane, 29.

Scheme III. Syntheses of (R)-(–)-isoflurane, 34, and (S)-(+)isoflurane, 35.
Scheme IV. Synthesis of atracurium besylate, 40.

Scheme V. Synthesis of rocuronium (bromide), 48.
Both secondary alcohols in tive opening of the second epoxy ring with morpholine, Correlation between Structure and Activity substrate being eight to one.

act, even with the initial molar ratio of alkylating agent to presume that the less basic morpholino nitrogen does not re-
diester with allyl bromide provides the pure stereoisomer reatives with p
43
α
from the rear (Scheme IV) can be understood as both a chemoselective and a stereo-
erates diene (Scheme V) is a steroid-based neuro-
muscular blocker that was designed so as to “incorporate acetylcholine-like fragments,” that is, MeCO2–C–C–NR 3
muscular blocker that was designed so as to “incorporate acetylcholine-like fragments,” that is, MeCO2–C–C–NR 3
Aware of the liver and kidney damage associated with chloroform anesthesia, hospital personnel were concerned that halothane, F3CCHBrCl, 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 debramination, 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:

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

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. A year later it was joined by a constitutionally iso-
meric 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:

$$\begin{align*}
19 & \rightarrow 49 \\
24 & \rightarrow \text{F}_2\text{CHOCF}_2\text{C} \equiv \text{Cl} \\
28 & \rightarrow (\text{CF}_3)_2\text{CHOH}
\end{align*}$$

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

Subsequent reaction of 49 or F₂CHOCF₂COCl with endo-
genous protein leads to impaired cellular chemistry
within the liver microsome and the appearance of
neoantigens:

$$\text{protein} \rightarrow \text{NH}_2 + 49 \rightarrow \text{CF}_3\text{CONH} \rightarrow \text{protein} \ (2)$$

Sevoflurane is the least problematic; not only is its degree
of degradation minimal but each of the fragments,
(CF₃)₂CHOH, CO₂, 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):

$$\text{FCH}_2\text{OC} \equiv \text{C} \equiv \text{CF}_2 \begin{array}{c}
\text{NaOH} \\
- \text{HF}
\end{array} \rightarrow \text{FCH}_2\text{O} \equiv \text{C} \equiv \text{CF}_2 \begin{array}{c}
\text{CF}_3 \\
\text{CF}_3
\end{array} \ (3)$$

Selection of an inhalant by an anesthetist is generally an
individual decision. Variation between the agents as to ra-
pidity of induction and recovery is modest. The vaporizers
in anesthesia machines are normally designed to handle liq-
uid 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 (ACh), 50, and (+)-tub-
ocurarine dichloride, 51, to serve as templates for the prepa-
ration 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 pres-
ence of one or more tetrakisalkylated aminium ions, R₄N⁺.
Also R₄N⁺ binds somewhat more strongly that does a
trisalkylated ammonium ion, R₃NH⁺. 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 hydro-
lytic 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).

**Gall Bladder Removal under Balanced General Anesthesia**

It has been established instrumentally (right upper quad-
rant or RUQ ultrasonography) and symptomatically (RUQ
pain precipitated by greasy and fatty foods) that gallstones
are responsible for a patient’s distress. Surgical removal of
the organ and stones is essential, and a minimally invasive pro-
cedure known as laparoscopic cholecystectomy is agreed to.
Morning surgery begins as the patient is positioned (reposed)
upon a gurney and immediately placed under sedation with
intravenous midazolam (1a). Before long the patient is
brought in to the operating room and transferred to a high-
tech operating table. A number of patient monitors are put
into place: an electrocardiogram, an automated blood pres-
sure sensor or cuff, a pulse oximeter, a skin temperature
monitor, a precordial stethoscope, and a BIS sensor. Bro-
genal anesthesia begins with 100% dioxygen though a loosely
fitting mask followed by intravenous injections (feeder line)
of the opioid analgesic fentanyl, the local anesthetic
lidocaine, to induce unconsciousness. Once the anesthesia
provider has confirmed that the patient is ventilating properly and
receiving ample oxygen from the anesthesia machine, the muscle relaxant rocuronium,
48, is supplied (injected) via a feeder line. A gas delivery (en-
dotracheal) tube is then inserted (intubated) into the trachea
or windpipe and immediately connected to a ventilator on
the anesthesia machine. Appropriate levels of dioxygen, ni-
trous oxide, and the inhalational anesthetic sevoflurane, 28,
are supplied (each monitored along with carbon dioxide) to
ensure effective treatment, augmented by readings from the
aforementioned patient monitors. Incremental doses of
rocuronium and fentanyl are supplied as indicated.8
Before long the diseased gall bladder has been removed through a
small incision just about the navel, and postoperative treat-
ment ensues. Nitrous oxide and sevoflurane are replaced with
100% dioxygen, so as to flush out residual anesthetic
in preparation for emergence. When sufficient muscle tone
and self-awareness has returned, the patient is extubated and
transferred to the recovery room.

**Notes**

1. Our basic references were: (a) Goodman, L. S.; Gilman, A.
   *Goodman & Gilman’s The Pharmacological Basis of Therapeutics*,
   9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon,
   and II. (c) Wilson, C. O.; Gisvold, O. *Wilson and Gisvold’s Textbook

![Figure 4. Compounds that served as templates for the preparation of synthetic neuromuscular blocking agents.](image-url)


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


