

Chemical Aspects of Local and Regional Anesthesia

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The formal debut of ether anesthesia on October 16, 1846 in Boston, Massachusetts (1) changed forever the nature of surgery and related procedures. From then on, general practitioners had access to a safe and painfree procedure to remove an abscessed molar or amputate a gangrenous limb. Today only an exceptional few Americans will pass through life without experiencing local (regional) or general anesthesia. It may be time to include anesthesia in Benjamin Franklin's well-worn cliché, "But in this world, nothing can be said to be certain, except for death and taxes" (2).

We begin with local anesthesia because it is less complicated than general anesthesia and fewer compounds are involved. General anesthesia will be addressed in two subsequent installments. The major focus of the three-part series is not on the biochemistry of anesthetic-body cell interaction; no all-inclusive mechanism is as yet available. Preference is given to the original syntheses¹ of the anesthetics. Inasmuch as the sedative-hypnotic midazolam and the opioid analgesic fentanyl are so often used during local anesthesia, their preparations are also included. Correlations of structure and activity are made when the available information is persuasive.² Two examples of hospital procedures involving regional anesthesia are given at the end.

The Onset of Local Anesthesia

The first local anesthetic was isolated from leaves of the coca shrub. Named cocaine,³ **1** (Figure 1), its first documented use in medicine occurred in 1884, when the ophthalmologist Carl Koller applied it to the surface of the eye. In 1892, the German chemist Einhorn took up the challenge of replacing this toxic and addictive substance with a suitable synthetic amino ester, even though questions regarding cocaine's structure were not completely answered until 1901 (3).

Preparation of Compounds

Einhorn's efforts culminated in 1906 with the preparation of procaine, **5**, (Scheme I)⁴ (4). Conversion of *p*-nitrobenzoic

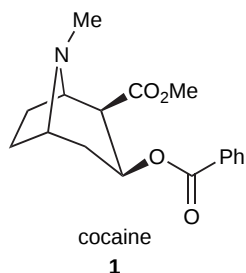


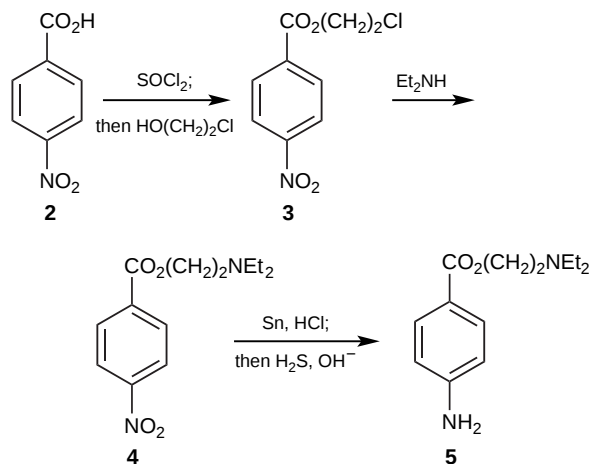
Figure 1. The first local anesthetic, **1**, was isolated from leaves of the coca shrub.

acid, **2**, to the chloroethyl ester **3** via the acid chloride was followed by S_N2 amination of the side chain with diethylamine to furnish intermediate **4**. Classical reduction of the ring nitro with an active metal completed the preparation of **5**.

A century later procaine is still used clinically, along with two derivatives, chloroprocaine, **7** (5), and tetracaine, **9** (Scheme II) (6). Conversion of 2-chloro-4-aminobenzoic acid, **6**, to **7** required only two steps, as did the transformation of *p*-aminobenzoic acid, **8**, to **9**. Ester formation is the second step in each case, and the alcohol co-reactant carries the required dialkylamino group, albeit in its protonated form. The chemoselective N-butylation of **8** reflects the enhanced nucleophilic character of the neutral amino group relative to the carboxylate ion.

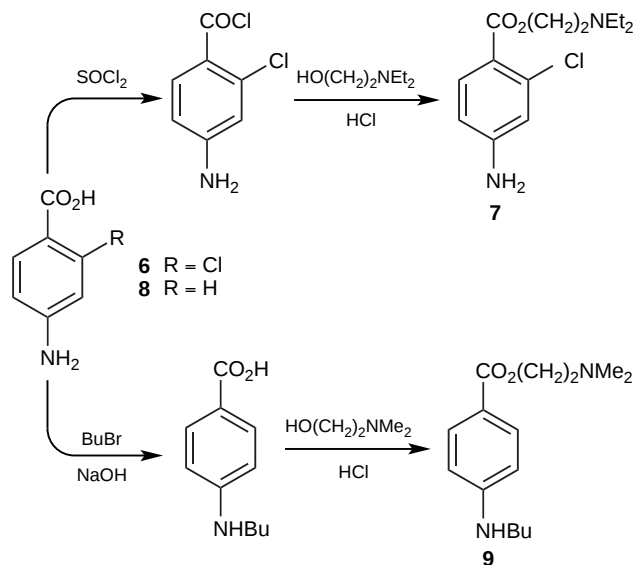
Ester-based local anesthetics such as procaine have largely been displaced by α-aminoamide compounds. The prototype lidocaine, **13**, (Scheme III) appeared in 1948 (7); the same chemistry led to analog **14**, etidocaine (Scheme III) (8), in due course. Formation of the α-chloroamides **11** and **12** of 2,6-xylylidine, **10**, was followed by direct displacement of the halogen with a secondary aliphatic amine as nucleophile to give, in turn, local anesthetics **13** and **14**.

Pivacaines **17**, **18**, and **19** (Scheme IV) are likewise derived from 2,6-xylylidine. Following acylation of **10** with 2-pyridinecarbonyl chloride, **15**, the α-amino moiety was unmasked via catalytic hydrogenation of the heterocyclic aromatic ring to form a common intermediate **16**. Individual names of the anesthetics were taken from the particular alkyl group attached in the final step, methyl sulfate leading to mepivacaine, **17** (9), propyl bromide to propivacaine, **18** (10), and butyl bromide to bupivacaine, **19** (9).

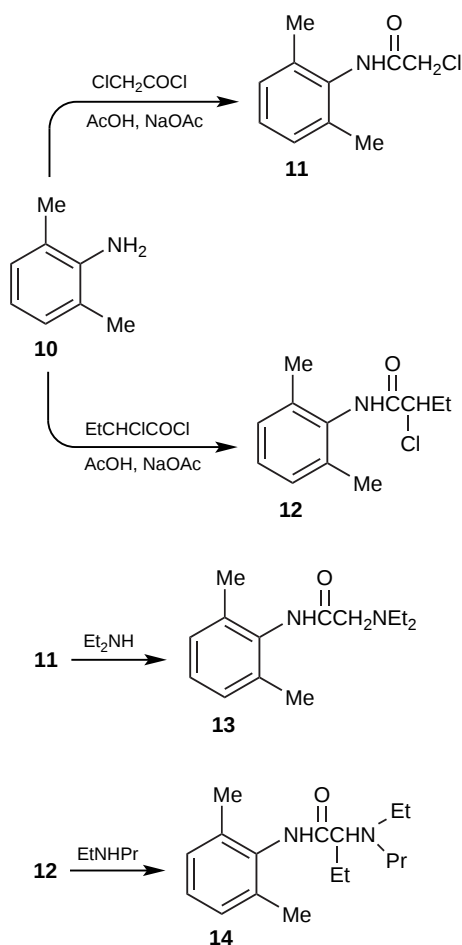


Scheme I. Synthesis of procaine, **5**.

Aqueous solutions of ester and amide anesthetics, commonly as the hydrochloride salts, are available in calibrated glass cartridges as well as in larger bottles, with individual



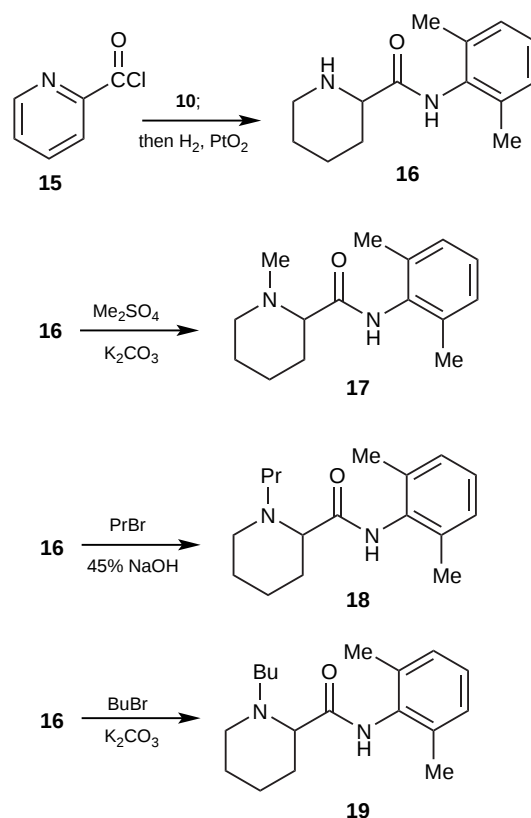
Scheme II. Syntheses of chlorprocaine, **7**, and tetracaine, **9**.



Scheme III. Syntheses of lidocaine, **13**, and etidocaine, **14**.

concentrations ranging from 0.25% to 4.0%. The vasoconstrictor epinephrine (adrenaline), **20**, or levonordefrin, **21** (Figure 2) is usually present as well, but in much lower concentration relative to the anesthetic: 1:50,000 to 1:200,000 for the more potent **20**, and 1:20,000 for its less potent constitutional isomer **21**.

We close with the preparations of fentanyl, **25** (Scheme V) (**11**), and midazolam, **31** (Scheme VI) (**12**), for it is not uncommon for patients to receive intravenous injections of these agents during noninvasive local or regional procedures. Fentanyl is an amide opioid that acts as a systemic pain reliever and a complement to the particular local anesthetic. Midazolam is a benzodiazepine sedative-hypnotic used to allay anxiety. In common with the pivocaines (vide supra) fentanyl contains a substituted piperidine ring. Reductive amination of 1-benzyl-4-oxopiperidine, **22**, with aniline led to diamine **23**. Subsequent amide formation (pyridine base) was followed by hydrogenolysis of the benzyl blocking group



Scheme IV. Syntheses of mepivacaine, **17**, propivacaine, **18**, and bupivacaine, **19**.

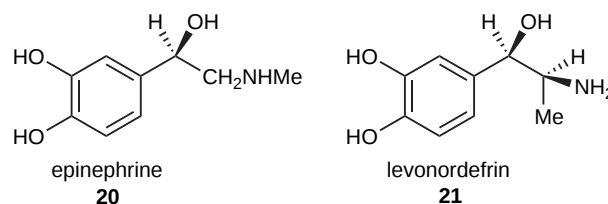


Figure 2. Structures of two vasoconstrictors.

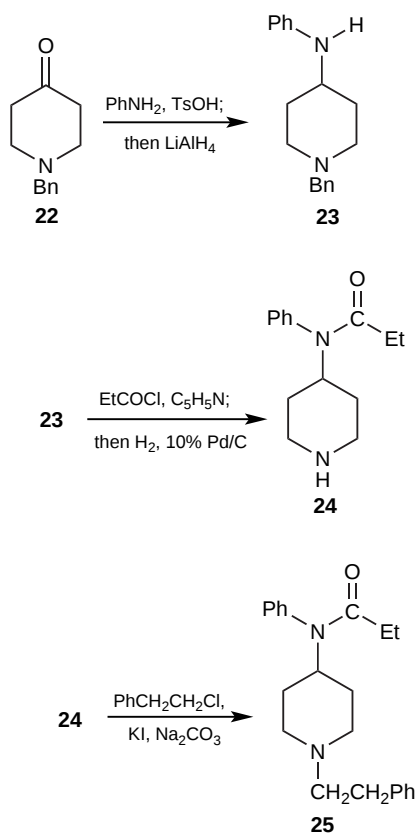
to arrive at the second intermediate **24**. Base-mediated N-alkylation of the piperidine ring with phenethyl chloride gave **25**.

The diazepine ring emerges first in the preparation of midazolam, **31**. Appending a glycyl group to the amino nitrogen of 2-amino-5-chloro-2'-fluorobenzophenone, **26**, provided the three atoms essential to the conversion of amide **27** to bicyclic **28**. Subsequent formation of the third (fused five-membered imidazole) ring was more complex. The workers chose to convert amide **28** into an amidine (N=C-N), that was subsequently modified by N-nitrosation so as to create an effective leaving group at C2 of the diazepine ring in **29**. Subsequent indirect displacement of an *N*-methyl-*N*-nitroso amide anion by the conjugate base of nitromethane was followed by catalytic hydrogenation to give vicinal diamine **30**. Ring closure of **30** with triethyl orthoacetate was straightforward; a final oxidation step with manganese dioxide completed the synthesis of **31**.

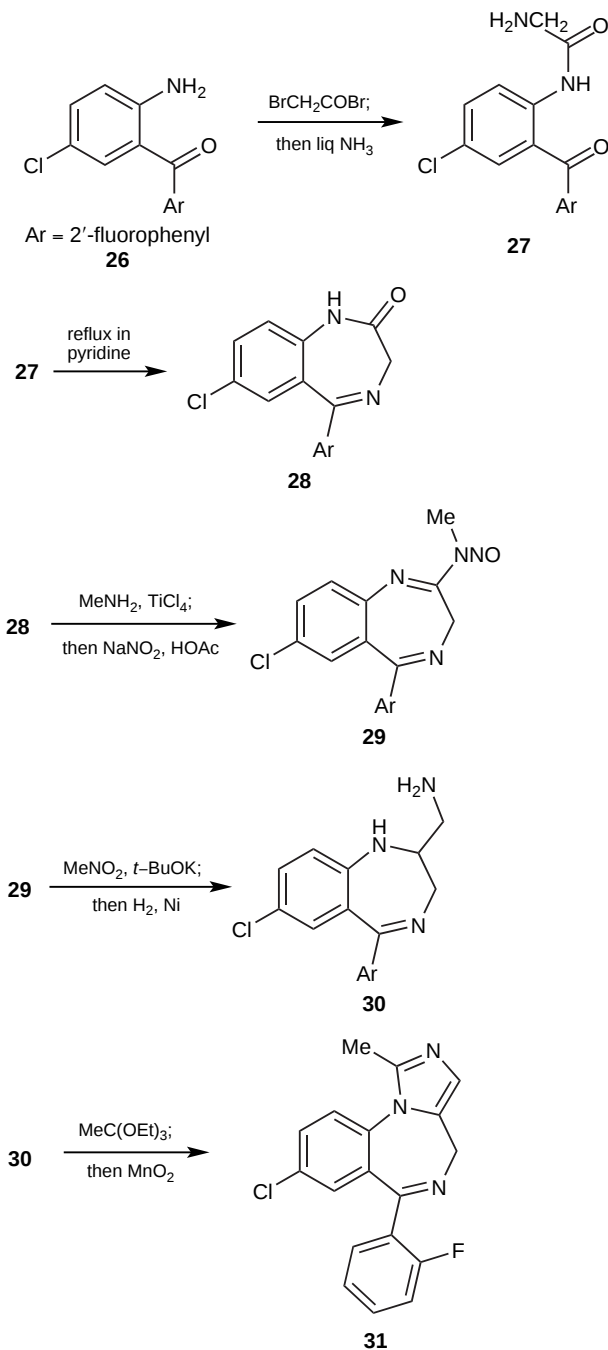
Correlation Between Structure and Activity

The most important effect of a local anesthetic must be on pain, first during the operation and, if needed, for an additional period of time. This action is almost certainly linked to the inhibition of ion channels in nerve cell membranes. As a signal (impulse) is being relayed to the brain, gated sodium ion channels in a localized portion, or axon, of each cell wall open and close. When the gate in a resting nerve cell opens, Na⁺ ions are pumped into the axoplasm,

thereby effecting the rapid decline (depolarization) of a potential gap between the inner and outer walls. Release of the neurotransmitter then follows, "setting off" the next cell in the series. Closing of the sodium ion channel precedes the restoration of a nerve cell to its original resting state and potential. The channel lining seems to be composed of complex glycosated proteins. The most widely accepted scenario involves the initial migration of the neutral (uncharged) anesthetic molecule through the nonpolar bilipid cell membrane, whereupon it enters the aqueous environment of the plasma. Protonation of the anesthetic then occurs and sub-



Scheme V. Synthesis of fentanyl, **25**.



Scheme VI. Synthesis of midazolam, **31**.

sequent migration of the cationic form (conjugate acid) into the ion channel and binding to the lining proteins inactivates the gate.

In this context let us examine the structural features of cocaine, **1**. Its lipophilic properties can be traced to the presence of a phenyl group and a hydrocarbon-based central skeleton. At the same time two ester groups and a tertiary aliphatic amino group provide hydrophilic sites. Presence of the amino group also ensures that a significant fraction of the anesthetic will exist in the protonated form (conjugate acid) under physiological conditions.

In a buffered system such as the blood, the equilibrium between a base B and its conjugate acid BH⁺ is succinctly summarized in the well-known Henderson–Hasselbalch equation:

$$\text{p}K_a = \text{pH} + \log \frac{[\text{BH}^+]}{[\text{B}]}$$

This relationship shows that if the pH of the blood is less than the $\text{p}K_a$, the major form of the local anesthetic in the plasma is a charged cation. If the $\text{p}K_a$ is less than the pH, then the uncharged molecular form is predominant. How this ratio responds to an in-channel encounter with a protein or to the nonaqueous lipophilic environment within the cell wall is not readily quantifiable, but the trend is clear. Current “successful” amide anesthetics (Schemes III and IV) possess $\text{p}K_a$'s,⁵ for example, 7.8 for lidocaine, **13**, and 8.1 for bupivacaine, **19**, that are close to the physiological pH 7.4. In the blood one in six molecules of bupivacaine remains unprotonated (uncharged), and so is able to make the journey through the cell wall. In comparison, the $\text{p}K_a$'s for ester anesthetics (Schemes I and II) are approximately one unit higher; thus, procaine, **5** (Scheme I), $\text{p}K_a$ 8.9, is 97% protonated and almost all the drug is trapped in a poorly diffusible ionized state. In practical terms, the onset of procaine anesthesia is slow compared to bupivacaine.

A tertiary aliphatic amino group with a $\text{p}K_a \sim 10.5$ is insufficient, for at a pH of 7.4 such a compound would be trapped as a cation. It is the additional presence of electron-withdrawing ester or amide groups that is responsible for the lower $\text{p}K_a$'s of local anesthetics. In cocaine, **1**, $\text{p}K_a$ 8.4, the amino nitrogen is two carbons removed from an ester carbonyl (C=O) and a third, additional carbon from a benzoyloxy group. Procaine, **5**, $\text{p}K_a$ 8.9, is a slightly stronger base with a terminal diethylamino group being coupled with a single *p*-aminobenzoyloxy group two carbons away. The greater acidity of protonated lidocaine, $\text{p}K_a$ 7.8, can be traced to the close proximity of the amide carbonyl. Insertion of a second methylene (–CH₂–) group between the carbonyl and the diethylamino group bumped the $\text{p}K_a$ up to 9.0 (homolidocaine, a β -amino-amide); with a third methylene the $\text{p}K_a$ increased further to 9.5.

The overall structure of the anesthetic is also important. The nonpolar environment within the cell wall was mentioned earlier. For proteins to be involved in regulatory functions, for example, in sodium ion channels, they must be prepared to bind to *polar and nonpolar* regions of a guest structure. This means that the impact of a local anesthetic is directly related to the *joint presence* of hydrophilic–lipophobic

amide, amine, and ester groups and lipophilic–hydrophobic aromatic rings and alkyls. Within the trio of amino esters **5**, **7**, and **9** (Schemes I and II) and also within the quintet of α -aminoamides **13** and **14** (Scheme III) and **17**, **18**, and **19** (Scheme IV), the small variations in $\text{p}K_a$'s are of minor significance. Structural changes do, however, alter lipophilic character and molecular size or shape, and so affect the manner in which an anesthetic binds to a receptor. The general guideline is that a local anesthetic with greater lipid solubility and a favorable (within a narrow range, vide infra) $\text{p}K_a$ will begin to act sooner and be longer lasting.

The ultimate destruction of a local anesthetic molecule will depend upon its effective rate of dissociation from the ion channel and its sensitivity to metabolism or deactivation. If these are minimal, one can expect the agent to be effective for long periods of time at relatively low dosage levels. Bupivacaine, **19**, is an example; it undergoes enzymatic degradation mainly in the liver. Presence of two flanking *m*-xylylidine derived methyls not only shields the inherently unreactive amide carbonyl from hydrolytic attack, but also seems to favor a strong binding interaction between **19** and the ion channel protein. In contrast the amino ester procaine, **5**, is an agent of minimal duration; the more reactive ester carbonyl is sterically unencumbered, and esterase mediated hydrolysis occurs in the plasma itself. Presumably **5** is also less tightly bound within the ion channel. Whereas the ester group and the aromatic ring in **5** are essentially coplanar, the amide carbonyl (and piperidine ring) in **19** and the alkylated benzene ring are not. The “twisted” conformation of bupivacaine may also contribute to the stronger interaction of **19** compared to procaine with the ion channel protein.

The ability of bupivacaine to bind with ion channel proteins can lead to cardiovascular problems, should the release of the anesthetic into the blood stream exceed a safe (low) level. Bupivacaine rapidly blocks sodium ion channels in heart muscle during systole, but during the diastolic phase (intake) it dissociates quite slowly. The block is cumulative and can abruptly lead to myocardial depression and ventricular arrhythmia. If cardiac toxicity is of serious concern, the anesthetist may choose to use the less toxic lidocaine, **13**, since it exchanges more rapidly with the heart muscle channel protein.

At the molecular level the (*S*)-(–) form of bupivacaine, **19**, shows an improved profile as to neural and cardiac toxicity versus the (*R*)-(+) enantiomer, as well as being longer lasting. This can be understood as the less tightly bound (*R*)-form of bupivacaine being released into the blood stream at a faster rate from the nerve cell, thence to find its way to the heart and the liver. In the end it would be the (*S*)-(–) form of propivacaine, **32**, renamed ropivacaine, that would be commercialized, based upon a lower toxicity with minimal loss in potency compared to (*S*)-**19**. Laboratory synthesis of propivacaine, **18** (Scheme IV) necessarily leads to a racemic mixture of **32** and its enantiomer (Figure 3). It is generally a routine, though not trivial, task to resolve a racemate into the two enantiomeric forms. In the present instance the resolution step may involve either intermediate **16** or propivacaine.

The genesis of fentanyl, **25**, can be traced to the naturally occurring pain reliever morphine, **33** (**13**). Close scrutiny of morphine reveals the inclusion of a piperidine moiety wherein the tertiary amino nitrogen is two sp^3 carbon atoms

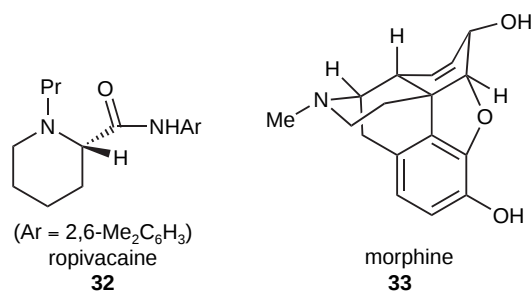


Figure 3. Structures of two commercial pain relievers.

away from a benzene ring. The analgesic fentanyl, **25**, retains this structural feature, augmented by an amide substituent at the opposite end of the piperidine core. With a pK_a of 8.3, fentanyl will undergo a significant degree of protonation in the blood. *Only after it has crossed the brain–blood barrier*, however, will this opioid become effective. The molecular form of midazolam, **31**, is highly lipophilic; with a pK_a of 6.0 it is not likely that the conjugate acid form plays an important role in the brain chemistry of **31**.

Regional Anesthesia in an Office or Hospital Operatory Setting

To illustrate the practical side of local or regional anesthesia, we now cite two applications of local anesthetics under moderately demanding circumstances. Our first example involves surgical repair of the severed lower tendon of the left index finger. Once the patient has been admitted to the ambulatory surgery unit, midazolam, **31**, and fentanyl, **25**, are given intravenously in the right arm, followed by a capped IV needle or cannula inserted into a vein in the back of the left hand. In sequence, a pneumatic tourniquet is positioned around the left upper arm and a rubber ace bandage is snugly applied to the elevated forearm to force as much blood as possible away from the region, followed by inflation of the cuff to 250 mm Hg pressure. Removal of the rubber ace bandage allows the blood vessels in the hand and lower arm to be partially refilled with 20 to 40 mL of 0.5% lidocaine, **13**, injected into the cannula. Once tendon repair is complete and all sutures are in place, deflation of the tourniquet restores circulation and the local anesthetic is washed out. Known commonly as Bier's block, this intravenous regional anesthetic (IVRA) procedure is also used in carpal tunnel syndrome surgery.

Our second example involves the delivery of a child. A pregnant woman in the early stages of cervical dilation and frequency of contraction arrives in the obstetrical ward. The mother-to-be has elected to have a labor epidural. The time arrives for the obstetrician and anesthesiologist to assist the patient. After receiving an intravenous dose of 500 mL to 1 L of lactated Ringer's solution, the patient is positioned so as to expose her lower back, and the area is cleansed and anesthetized with lidocaine, **13**. Next an epidural needle is positioned between two lumbar vertebrae. A smaller catheter, passed through the needle, remains in place when the needle is withdrawn. Continuous infusion of a blend of bupivacaine,

19, and fentanyl, **25**, via the epidural catheter is provided by a programmable pump.

Acknowledgment

We wish to thank a referee for drawing our attention to *Wilson and Gisvold's Textbook of Organic, Medicinal, and Pharmaceutical Chemistry*.²

Notes

1. U.S. patents accessible online and direct print copies can be made starting with patent number 3,930,271 (Jan 6, 1976) at <http://patft.uspto.gov/netacgi/nph-Parser?patentnumber=3930271> (accessed Aug 2006).
2. Our basic references were: (a) Goodman, L. S.; Gilman, A. G. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon, R. W., Eds.; McGraw-Hill: New York, 1996. (b) *Anesthesia*, 4th ed.; Miller, R. R., Ed.; Churchill Livingstone: New York, 1994; Vols. I and II. (c) Wilson, C. O.; Gisvold, O. *Wilson and Gisvold's Textbook of Organic, Medicinal, and Pharmaceutical Chemistry*, 11th ed.; Block, J. H., Beale, J. M., Jr., Eds.; Lippincott, Williams, and Wilkins: Baltimore, MD, 2004.
3. All such nonsystemic names are those found in *The Merck Index*, 13th ed.; O'Neil, M. J., Smith, A., Heckelman, P. E., Budavari, S., Eds.; Wiley: New York, 2001.
4. The efficient placement of structural information in schemes and elsewhere is facilitated by using the following abbreviations: Me = methyl, Et = ethyl, Ac = acetyl, Pr = propyl, Bu = butyl, *t*-Bu = *tert*-butyl, Ph = phenyl, Bn = benzyl, and Ts = tosyl.
5. Literature pK_a values can be at 20 °C, 25 °C, or 37 °C (normal body temperature). At the higher temperatures, a value is generally smaller by 0.1 (25 °C) or 0.2 units (37 °C).

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