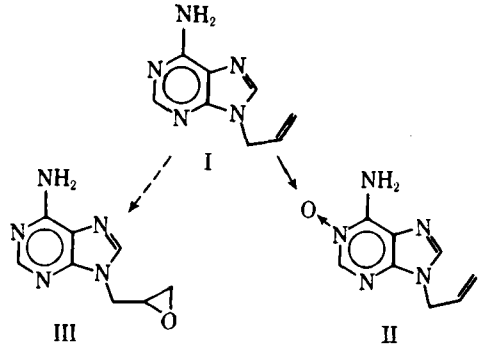
Synthesis of 9-Allyladenine N^1-Oxide

Keyphrases □ Allyl adenine N^1-oxide—chemical synthesis □ Hypolipidemic agents—allyl adenine N^1-oxide, chemical synthesis

To the Editor:

During our investigations of novel hypolipidemic agents (1), we desired to synthesize 9-(2,3-epoxypropyl)adenine (III) by the reaction of *m*-chloroperoxybenzoic acid with 9-allyladenine (I) as described previously (2). Compound III was not obtained, although the decomposition point and NMR data in trifluoroacetic acid were consistent with the literature (2). For comparison, the spectrum of I in trifluoroacetic acid was taken. No difference in the chemical shifts of the protons in the side chain between I and the oxidized material was observed (Scheme I). However, there was a difference in the ring protons.



Scheme I

A spectrum of the oxidized material in dimethyl sulfoxide-d_6 was obtained by using a Fourier transform NMR (650 scans, saturated 1.5-ml sample). This spectrum was consistent with the N^1-oxide (II). A shift downfield of the C_2 ring proton and a splitting of the nitrogen protons occurred[1]. The fact that no change in the chemical shift of the olefinic protons in dimethyl sulfoxide-d_6 was observed establishes this material as the N^1-oxide. This product also is more consistent with the literature, since peroxidation of 9-substituted adenines using hydrogen peroxide or *m*-chloroperoxybenzoic acid gives the N^1-oxide (3).

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[1] Fourier transform NMR (dimethyl sulfoxide-d_6): δ 8.58 and 8.23 (2s, 2, adenine CH), 7.89 and 7.59 (m, 2, NH_2), 6.05 (m, 1, olefinic CH), 5.23 (m, 2, olefinic), and 4.82 (m, 2, CH_2). Analyzed ($C_8H_9N_5O$) for carbon, hydrogen, and nitrogen.

Temperature-Dependent Aqueous Solubilities of Lidocaine, Mepivacaine, and Bupivacaine

Keyphrases □ Lidocaine—aqueous solubility, effect of temperature □ Mepivacaine—aqueous solubility, effect of temperature □ Bupivacaine—aqueous solubility, effect of temperature □ Local anesthetics—aqueous solubility, effect of temperature

To the Editor:

We previously prepared 3-hydroxy-2-naphthoates of lidocaine, mepivacaine, and bupivacaine to prolong the duration of action of these local anesthetics through their sparingly soluble salt forms and studied their dissolution characteristics at 37° in 0.7 *M* phosphate buffer, pH 7.46 (1). Only the bupivacaine salt exhibited unusual dissolution characteristics. At equilibrium, the solution was saturated incongruously with respect to the base and the acid component. Further studies with the bupivacaine salt at 25° showed no such unusual behavior. The unusual behavior at 37° resulted from the fact that the concentration of the base component dissolved out of the solid salt exceeded the solubility of the base at 37° (2).

These observations prompted us to examine the temperature dependency of aqueous solubilities of bupivacaine and its structural analogs, lidocaine and mepivacaine. The only available data on the solubility of these local anesthetics at different temperatures were those of Setnikar (3), who reported lidocaine solubility in an alkaline medium to be 16 m*M* at 20° and 15 m*M* at 37°.

Lidocaine base[1] and mepivacaine base[2] were used as received. Bupivacaine hydrochloride[2] was converted to the base for solubility determination. Excess base was placed in a 20-ml glass-stoppered test tube together with a small magnetic stirring bar. Two milliliters of either 0.5 *M* phosphate buffer[3], pH 7.4[4], or 1–4 m*M* NaOH was added to it. The test tube was placed in a jacketed beaker and mounted on the platform of a magnetic stirrer, together with a magnet bar and water. The water temperature inside the jacketed beaker was maintained constant with water circulated through the jacket by a constant-temperature circulator[5].

After equilibration for 16–48 hr at different temperatures, the solid phase was separated by vacuum filtration through a glass filter. All glassware used in the filtration process and subsequent sampling was preincubated to the study temperature. The filtrate was suitably diluted for spectrophotometric assay for lidocaine and mepivacaine at 262 nm. The bupivacaine equilibrium concentration was determined, after extraction with methylene chloride, by GLC[6], using a 3% OV-17 column (4) and mepivacaine as an internal standard.

As with bupivacaine (2), lidocaine and mepivacaine showed decreases in solubility with increasing temperature

[1] Fujisawa Pharmaceutical Co., Osaka, Japan.
[2] Yoshitomi Pharmaceutical Industries, Osaka, Japan.
[3] Composition at the time of preparation was 0.427 *M* Na_2HPO_4 and 0.0710 *M* NaH_2PO_4.
[4] Digital 112 research pH meter, Corning Scientific Instruments, Medfield, Mass.
[5] Haake model FK 10.
[6] Shimadzu model GC-4BM gas chromatograph.

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Table I—Temperature-Dependent Solubilities [a] (Millimolar) of Lidocaine, Mepivacaine, and Bupivacaine in 0.5 *M* Phosphate Buffer, pH 7.4 [b], and 1–4 m*M* NaOH [c]

Temperature [d]	Lidocaine		Mepivacaine		Bupivacaine	
	0.5 *M* Phosphate Buffer	1–4 m*M* NaOH	0.5 *M* Phosphate Buffer	1–4 m*M* NaOH	0.5 *M* Phosphate Buffer	1–4 m*M* NaOH
14.5°	30.3 ± 1.4	—	17.1	—	1.35	—
14.9°	—	18.5 ± 0.5	—	13.6 ± 0.3	—	0.375 ± 0.003
25.0°	22.9 ± 0.1	16.3 ± 0.1	13.5	10.2 ± 0.4	0.850 ± 0.020	0.318 ± 0.002
34.5°	—	14.6 ± 0.1	—	9.91 ± 0.20	—	0.313 ± 0.004
37.0°	16.5	—	9.90	—	0.575 ± 0.008	—

[a] Either the result of a single determination or average (two or three determinations) ± *SE*. [b] Composition at the time of preparation was 0.427 *M* Na_2HPO_4 and 0.0710 *M* NaH_2PO_4, pH 7.40 ± 0.01 at 25° and 7.38 ± 0.01 at 37°. [c] The pH varied from 10.43 (1 m*M* at 34.5°) to 11.86 (4 m*M* at 14.9°). [d] Temperature control was ±0.1°.

in the phosphate buffer (Table I). Since the pKa of these bases varied at 23° from 7.78 for mepivacaine to 8.09 for bupivacaine (5), at pH 7.4 these local anesthetics existed as a mixture of protonated and unprotonated forms. Thus, the solubilities of the unprotonated base species were determined in 1–4 m*M* NaOH. The solubilities in these high pH media were independent of hydroxyl-ion concentration and increased with decreasing temperature (Table I), although this trend was not as great as in the phosphate buffer.

The difference in temperature dependency is now being studied in our laboratories and is probably due to a measurable decrease in the pKa values of the bases with increasing temperature whereas the phosphate buffer pH remains relatively constant (Table I, footnote *b*). Our preliminary determination of lidocaine pKa values at different temperatures by the solubility method indicated that they vary from 8.2 at 15° to 7.7 at 35°. With increasing temperature, therefore, the gap between the medium pH and the pKa diminishes. Thus, the proportion of the soluble protonated base, BH^+, decreases with increasing temperature, which is reflected greatly in the total solubility, S_t, of the base at pH around 7.4; *i.e.*, S_t is given by (6):

$$S_t = [B] + [BH^+] = S_0\left(1 + \frac{[H^+]}{K_a}\right) \qquad \text{(Eq. 1)}$$

where $[B] = S_0$ is the solubility of the unprotonated species and K_a is the acid dissociation constant of BH^+. Since S_0 decreases and K_a increases as the temperature is increased (Eq. 1) at pH 7.4, both of these effects contribute to lower solubility at higher temperatures.

Since the unusual temperature-dependent solubility is likely to extend over a fairly wide pH range, including physiological pH, the following clinical problem could arise. In parenteral dosage forms of these drugs as local anesthetics, solution is effected by means of their hydrochloride salts. Therefore, the pH of these preparations can be as low as 3.0–4.5 (7). The results of the present study suggest possible precipitation of the base at the injection site from the following two points: (*a*) an increase in pH to the tissue pH after injection, as was suggested earlier for lidocaine (8); and (*b*) a lowering of free base solubility at body temperature relative to ambient temperature.

For most organic compounds, solubilities are usually assumed to increase with temperature. These local anesthetics, however, behave differently. Even if the decrease in solubility with increasing temperature at pH values of around 7.4 is mainly attributable to a decrease in the fraction of protonated species because of a shift in pKa with increasing temperature, the unprotonated species also show atypical temperature-dependent solubilities. Only a few organic medicinal compounds are known to exhibit such behavior. These include anhydrous ampicillin (9), dactinomycin (10), aminopyrine and propyphenazone (11), and colchicine (12).

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Carbocyclic Analog of Cytarabine

Keyphrases □ Cytarabine, analogs—synthesis, carbocyclic analog, antileukemic activity □ Antineoplastic agents—cytarabine, carbocyclic analog, synthesis □ Antineoplastic activity—cytarabine, carbocyclic analog

To the Editor:

Cytarabine (1-β-D-arabinofuranosylcytosine, Ara-C) inhibits a variety of experimental neoplasma (1, 2), produces remissions in some patients with acute myelocytic or acute lymphocytic leukemia (3–5), and is considered the most effective single-drug treatment for acute myelogenous leukemia (6). It is also effective in suppressing the replication of certain DNA viruses (2) and is a useful agent for the clinical treatment of herpes virus infections (7). Recently, we reported (8) the synthesis and activity of the carbocyclic analog (carbodine, I) of cytidine against a murine leukemia (L-1210). Brockman *et al.* (9) showed that carbodine inhibits both DNA and RNA synthesis in

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