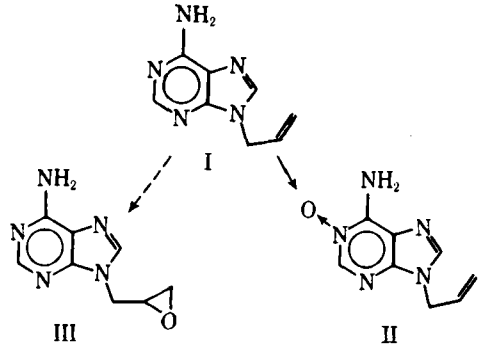
Synthesis of 9-Allyladenine N^1-Oxide

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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(2) K. Kondo, K. Kuwata, and K. Takemoto, *Makromol. Chem.*, **160**, 341 (1972).

(3) J. P. Miller and R. K. Robins, *Ann. Rep. Med. Chem.*, **11**, 291 (1976).

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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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