talis-like effect on the heart. Subsequently, Ten Ham *et al.* (2) reported that the cardiac action of an ethanol–water extract (50% alcohol) of *Cannabis* roots was due solely to the potassium content of an infused extract (140 mmoles). This action was exemplified by the following changes in the guinea pig ECG: bradycardia, T wave and QRS complex inversion, and recovery of the heart when infusion was discontinued. We wish to report our preliminary findings indicating the presence of substances other than potassium in *Cannabis* roots of Mexican origin[1] that display cardiac activities.

Dried, ground root material was percolated consecutively with hexane, chloroform, 95% ethanol, water, and 5% hydrochloric acid. The potassium content of the first four extracts prepared for infusion[2] was determined by atomic absorption spectroscopy and found to be 0.109, 0.181, 16.9, and 36.0 mmoles, respectively[3]. Ten Ham *et al.* (2) reported the potassium content of their infusion-prepared ethanol–water extract by flame photometery to be 140 mmoles/liter. Cardiac activity, although different from that observed by Ten Ham *et al.* (2), was found in the hexane, chloroform, and ethanol extracts; however, no activity of a detrimental nature was observed in the aqueous or 5% hydrochloric acid extracts.

Cardiac screening was done using anesthetized male guinea pigs. The right jugular veins were cannulated with polyethylene tubing to a distance of approximately 1 cm from the heart. Infusion of the dried extracts (emulsified in 2% sorbitan ester[4], 3% polysorbate 60, and 4% ethanol in water)[2] was then carried out at the rate of 0.2 ml/min and was continued until the heart stopped or for 90 min. The ECG was monitored through bipolar leads attached on either side of the thorax at the base of the front limbs[5].

For each extract, the ECG of a vehicle-only control animal was recorded which showed slight bradycardia, an increase in the PR interval, and an increase in the QRS complex amplitude. The hexane extract was fractionated into polar and nonpolar portions[6]. The cardiac activity was mainly associated with the less polar fraction which contained insignificant traces of potassium. Infusion of the hexane extract had a rapid and pronounced effect on the heart. Bradycardia, prolonged PR intervals, and A–V conduction blockade developed quickly. After 18 min, atrial activity had disappeared, with death occurring following 23 min of continuous infusion of the extract. The chloroform extract[2] produced effects similar to those caused by infusion of a 140-mmole solution of potassium chloride, as described previously (2); however, there was no inversion of the T wave. The A–V conduction was severely impaired and the heart irreversibly stopped. The ethanol extract[2], in addition to causing irreversible heart stoppage, produced a more pronounced arrhythmia than any other extract; during later stages of infusion, a prominent conduction blockade was observed within 10 min after the appearance of multiple P waves. The heart then entered a short period of ventricular fibrillation and collapsed. Once definite arrhythmias were observed, termination of infusion did not stop the progressive deterioration of the heart.

The aqueous and 5% hydrochloric acid extract infusions[2] were apparently not toxic and, indeed, when compared with the control animals receiving the suspension vehicle alone, fewer changes in the ECG were observed. Bradycardia was not seen, but three of four subjects showed an increase in heart rate of 25–40%.

These preliminary data strongly suggest that *Cannabis* roots of Mexican origin do contain organic component(s) that produce cardiac activities quite different than those classically observed with potassium ions. It is quite possible that Mexican *Cannabis* roots contain chemicals not found in other "variants." This is the case for the cannabinoids (3, 4). Thus, this could explain the difference in findings by Ten Ham *et al.* (2) and our group. Further fractionations of these extracts are underway in an effort to isolate the principle(s) responsible for the observed cardiac activities.

[1] Mexican roots from plants grown on the University of Mississippi campus in 1972. Voucher specimens are located in the *Cannabis sativa* L. Herbarium, School of Pharmacy, University of Mississippi.

[2] Concentration of extracts was 18.4 mg/ml.

[3] Jarrell Ash dual-atom atomic absorption spectrograph.

[4] Arlacel.

[5] Beckman RN dynograph.

[6] Concentration of fractions prepared for infusion was 9.2 mg/ml each.

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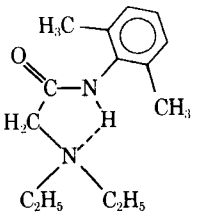
Lidocaine: A Case of Intraamide Hydrogen Bonding

Keyphrases □ Lidocaine—spectroscopic data supporting intraamide hydrogen bonding, *trans*-planar configuration □ Hydrogen bonding—spectroscopic data supporting lidocaine intraamide hydrogen bonding, *trans*-planar configuration

To the Editor:

In 1969, Neville and Cook (1) described some interesting and unusual spectroscopic data on lidocaine (2-diethylamino-2′,6′-acetoxylidide). These data were interpreted in terms of a *cis*-amide configu-



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ration for the molecule and dimerization by intermolecular hydrogen bonding.

Related data were obtained in this Institute following some IR studies on the effect of systematically changing the steric and polar properties of R and R′ on the configurational and hydrogen bonding properties of the amide group in *N*-alkylamides and benzanilides of the general type R—CONH—R′. In some of these molecules, *cis*- and *trans*-forms of the amide group exist in equilibrium with one another in dilute solution (2, 3). But if an attractive polar interaction is introduced between an electronegative atom in the R group and the amido hydrogen, the *trans*-planar configuration of the —CONH— group is stabilized to the exclusion of the *cis*-configuration (3).

In the lidocaine molecule, there is a possibility of polar interaction between the nitrogen atom of the 2-diethylamino group and the amido hydrogen. Three 2′,6′-xylidides [$RCONHC_6H_4(CH_3)_2$, in which R = $CH_3CH_2CH_2$, CH_3OCH_2, and $(C_2H_5)_2NCH_2$] were prepared, and the IR spectra of 0.001 *M* solutions of these compounds in carbon tetrachloride were recorded.

The spectrum of butyro-2′,6′-xylidide shows sharp symmetrical NH-stretching bands at 3433 and 3387 cm^{-1} arising from the monomeric *trans*- and *cis*-forms (4) of the amide group, respectively. However, if there is an electronegative oxygen atom in the 3-position as in methoxyaceto-2′,6′-xylidide, a single band is observed at 3401 cm^{-1}. This band is attributed to intramolecular interaction between the ether oxygen and the amido hydrogen atom by analogy with benzxylidide [$C_6H_5CONHC_6H_4(CH_3)_2$] and its 2-fluoro analog (3). In both cases the attractive interaction resulting from the introduction of an electronegative atom at R while simultaneously minimizing steric changes results in further stabilization of the *trans*-configuration of the —CONH— group so that the *cis*-form is not observed. The broad absorptions near 3300 and 3200 cm^{-1}, which normally arise from multimeric *trans*- or *cis*-forms of the amide group (4), are absent from the spectrum of both the butyro- and methoxyacetoxylidide at the 0.001 *M* concentration used throughout this study.

The carbon tetrachloride solution spectrum of lidocaine shows, in contrast, a broad symmetrical NH-stretching absorption at 3320 cm^{-1} confirming the observation described by Neville and Cook (1). No sharp bands due to monomeric *cis*- or *trans*-forms are observed near 3400 cm^{-1}, as would be expected by analogy with the butyro and methoxyaceto compounds. Both the absence of sharp monomer bands and the breadth of the NH-stretching band, as well as its position, are attributed to intramolecular interaction between the lone pair electrons on the tertiary amino nitrogen and the amido hydrogen (I) stabilizing the *trans*-planar configuration of the amide group.

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Effects of Hydraulic Pressure and Nozzle Orifice Size on Delivery Rates of Sprayed Materials

Keyphrases □ Spray processes—effects of hydraulic pressure and nozzle orifice size on delivery rates □ Delivery rates, sprayed materials—effects of hydraulic pressure and nozzle orifice size □ Coating processes—effects of hydraulic pressure and nozzle orifice size on delivery rates of sprayed materials

To the Editor:

Spraying processes are important in many phases of the development and production of certain pharmaceutical dosage forms. The manner in which these processes are carried out can affect the physical appearance, stability, and bioavailability of the product. Therefore, the judicious choice of nozzle size and hydraulic pressure for a particular process should improve product uniformity as well as batch-to-batch reproducibility.

A practical equation derived from fundamental flow theories (1–3) applicable to an airless spray system is:

$$R = KD^2\sqrt{\frac{P}{\rho}} \qquad \text{(Eq. 1)}$$

where R = volumetric rate of fluid delivery, D = diameter of nozzle orifice, P = hydraulic pressure, ρ = density of material, and K = proportionality constant. This equation predicts that the flow rate is directly proportional to the cross-sectional area of the nozzle orifice and to the square root of pressure. Also, flow is inversely proportional to the square root of the density of the liquid. Therefore, graphs of flow rate *versus* square root of pressure, diameter