β-carbolines, both quaternary and tertiary (X-XIII), completely lack the inhibitory activity. The influence of indole-*N*-methylation on the anticholinesterase activity is greater with the quaternary aromatic β-carbolines than with the tertiary series. The activity is either absent or greatly reduced in indole-*N*-methylated quaternary β-carbolines. An oxygen function at C-6 (as in III) potentiates the inhibitory activity, but oxygenation at C-7 (XIV) considerably reduces it. The effect of extended conjugation on the anticholinesterase activities is revealed by the greater potency of sempervirine (XVII) compared to either alstonine (XV) or serpentine (C_{20}-epimer of alstonine). In the case of nonaromatic β-carbolines, *e.g.*, alstoniline (XVI), the degree of conjugation is without any effect.

These observations seem to indicate that the primary structural requirement for the anticholinesterase activities of the β-carbolines is a resonance stabilized-type (XIX) species. The lack of inhibitory activity noted with the tetrahydro-β-carbolines suggests a limited affinity of the molecule for the enzyme, the binding being only at one site, *i.e.*, tertiary or quaternary nitrogen. In the case of the quaternary aromatic β-carbolines a two-point inhibitor–enzyme attachment (XIX) could be visualized: one at the anionic site between the enzyme carboxyl group and the quaternary nitrogen of the inhibitor and the other at the esteratic site in the form of hydrogen bonding by the hydroxyl of the enzyme serine and the anionic indolic nitrogen. Other forces may also be operative, including the degree of extended conjugation of the inhibitor molecule. Thomas and Marlow (14) reported that there was a regular increase in the inhibitory potencies of the "aromatic-type" compounds (*i.e.*, compounds containing quaternary nitrogen in an aromatic ring) with the increase in the conjugated chain length. The phenomenon can be explained in terms of charge delocalization and favorable stereochemistry for binding of the inhibitor to the enzyme. A parallel was observed in the greater anticholinesterase potency of sempervirine (XVII) compared to either alstonine (XV) or serpentine.

The almost equal potencies noted for alstonine and serpentine suggest that the stereochemistry of the D/E rings of the indole alkaloids is without any influence on the anticholinesterase activities of the β-carbolines.

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▲ To whom inquiries should be directed.

COMMUNICATIONS

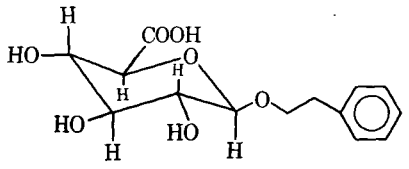
Direct Synthesis of a Glucuronide: Specific Complexing of Copper among Biological Cations

Keyphrases □ Glucuronides—direct synthesis of phenethyl-β-D-glucopyranosiduronic acid □ Phenethyl-β-D-glucopyranosiduronic acid—direct synthesis, complexation with copper □ D-Glucuronic acid—synthesis of phenethyl alcohol glucuronide □ Copper complexation—with phenethyl-β-D-glucopyranosiduronic acid

Sir:

The synthesis of glucuronides ordinarily requires several steps with frequently poor yields. I wish to report a synthesis of phenethyl-β-D-glucopyranosiduronic acid (I) in 52% yield directly from the alcohol and D-glucuronic acid.

A mixture of 30.0 ml. of phenethyl alcohol (0.25 mole) and 10.0 ml. of methanesulfonic acid was cooled to room temperature. To this was added 9.7 g. of D-glucuronic acid (0.05 mole); the slurry was stirred at room temperature for 7.5 hr., during which time most of the D-glucuronic acid dissolved. (Under comparable conditions, methanol reacted in 0.5 hr. and phenol in 2 hr., although in these instances the products were not isolated.) The nearly clear mixture was added to 200 ml. of 1 *M* sodium bicarbonate and extracted with ethyl acetate. Evaporation of the ethyl acetate at 25° in vacuum gave an oily residue. At this point the preparation was relatively clean, since TLC using ethyl acetate and silica gel showed only two components: a major one at R_f 0.57 and a minor one at R_f 0.73. The presumed esteruronide was hydrolyzed by stirring with a solution of 7.90 g. (0.025 mole) of barium hydroxide octahydrate in 200 ml. of water for 0.5 hr. Barium was removed by



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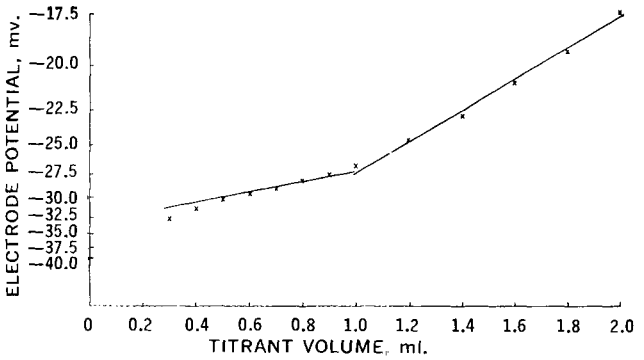

Figure 1—*Grans plot titration of 20 ml. of 10^{-3} M potassium phenethyl-β-D-glucopyranosiduronate with 10^{-2} M $CuCl_2$. Background: 10^{-1} M potassium acetate.*

addition of the calculated amount of potassium sulfate (4.35 g., 0.025 mole, in 40 ml. of water) and filtering. By evaporating the filtrate and crystallizing from methanol and ethanol, 8.81 g. of crystalline potassium salt was obtained. It was characterized by analysis and specific IR absorption peaks. The presence of the β-glucopyranosido grouping was indicated by the triplet at 796, 875, and 928 cm.$^{-1}$.

By using a monovalent cation electrode[1], the product was checked for complexing of potassium ion at pH 7.8 in the concentration range of 2.36×10^{-4} to 2.36×10^{-2} *M* but no complexing was found. A portion was converted to the sodium salt by ion exchange and examined similarly but no complexing was found. Grans plots[2] were then made using a divalent cation electrode[3], a 10^{-3} *M* solution of the glucuronide potassium salt containing a background of 10^{-1} *M* potassium acetate to act as pH and ionic strength adjuster, and 10^{-2} *M* titrants of Ca^{+2}, Mg^{+2}, Fe^{+2}, Zn^{+2}, Cu^{+2}, Co^{+2}, and Mn^{+2} (all as the chlorides). Negative results for complex formation were found in every case except Cu^{+2}, which showed a break in the titration curve (Fig. 1) at a ratio of 1:1 Cu^{+2}–phenethyl-β-D-glucopyranosiduronate. Complex formation was confirmed (after isolation from a 10^{-3} *M* solution at pH 7.65) from the IR spectrum of the green glass complex and analytical data for the ratio of copper to carbon. Thus, among the major biological cations, copper is specifically bound by this glucuronide in dilute solution at a pH close to that of blood.

Glucuronides as a class may be favorable materials for manipulating cations in living systems, because they are reported to be not metabolized and not rapidly excreted (1). Other indications for complex formation in this group may be stilbestrol glucuronide (an unusually insoluble sodium salt) and euxanthic acid (isolated as a magnesium salt). Finally, it should be pointed out that phenethyl alcohol is a natural antibiotic (2) active against bacteria and molds in the concentration range of 0.25–0.30% (3). It has been shown (4) to inhibit RNA and protein synthesis. There is a possibility that phenethyl alcohol *in vivo* is converted to its glucuronide which, in turn, inhibits a key copper-dependent enzyme such as cytochrome oxidase.

[1] Catalog No. 476220, Corning Glass Works.
[2] A 10% volume corrected paper was used; Catalog No. 90-00-90, Orion Research Inc.
[3] Model 92-32, Orion Research, Inc.

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JAMES G. MURPHY
National Institute of Arthritis and Metabolic Diseases
Bethesda, MD 20014

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Prediction of Dissolution Rates of Slightly Water-Soluble Powders from Simple Mathematical Relationships

Keyphrases ☐ Dissolution rates, slightly water-soluble powders—prediction from simple mathematics ☐ Powders, slightly water soluble—dissolution rates predicted from simple mathematics

Sir:

Recently, several articles in the literature reported sophisticated, expensive, and complex methods for determining the dissolution rates of slightly water-soluble powders (1–3). Aside from the fact that these and similar methods require the development of sensitive analytical procedures, the results obtained are often unpredictable. For example, Ullah and Cadwallader (1) were unable to detect differences in the rate of dissolution of salicylic acid ranging in particle size from 60 to 230 mesh. This is contrary to the fact that the rate of dissolution depends on the exposed surface area of the drug. I wish to report that one can predict, with high accuracy, the rate of dissolution of powders from simple mathematical relationships. The only required information is: (*a*) the surface area of the powder, and (*b*) the solubility of the compound in the dissolution media.

The amount of drug dissolved under sink conditions

Table I—Diffusion Coefficients of Weak and Nonelectrolytes in Water at 25°

Solute	$D \times 10^5$ cm.^{2}/sec.
Glucose	0.67
Pentaerythritol	0.76
Glycolamide	1.14
α-Alanine	0.91
β-Alanine	0.93
o-Aminobenzoic acid	0.84
Aminobenzoic acid	0.84