tographically pure PNPG was present in a small quantity and accounted for about 1–2% of the urinary metabolites. We also noted from our experiments that 24–50% of the administered PNP was excreted in urine in the form of metabolites of PNP in the first 5 hr., and that PNPGA and PNPS were the major products detectable on chromatograms at that time. The two metabolites accounted for about 95% of the urinary metabolites. This observation is in accord with an earlier work of Robinson *et al.* (2). In the 5-hr. urine, PNPGA and PNPS appeared to be present in equal amounts.

The fact that PNPG was present only in small amounts in the urine explains why the metabolite eluded detection in the past. However, low urinary excretion need not necessarily imply low production of this metabolite at all times in the body, but may be related to the fact that PNPG is not sufficiently acidic for extensive renal excretion. *In vitro*, the glucosylation pathway appears quite active (1). In this context perhaps it is significant that *N*-acetylglucosamine conjugation of steroids is also a pathway that appears to be very active *in vitro* (3), but such metabolites are detected with difficulty in mammalian urine (4).

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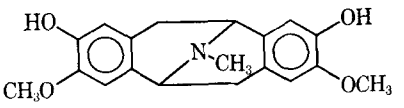
Total Synthesis of (±)-Bisnorargemonine

Keyphrases ☐ (±)-Bisnorargemonine—synthesis ☐ IR spectrophotometry—identification ☐ UV spectrophotometry—identification ☐ NMR spectroscopy—identification ☐ Mass spectroscopy—identification

Sir:

We had previously (1) postulated Structure I for bisnorargemonine based on its unambiguous NMR spectrum, in which the chemical shifts of the aromatic and methoxyl protons appeared to be unequivocal for the structural assignment. Nevertheless, since a structure based on spectral evidence alone should be substantiated by synthesis, we have completed the necessary synthesis



I

by a 14-step procedure and an alternate 16-step procedure.

In the shorter synthesis, we started with the preparation of *O*-benzylvanillin, which was condensed with hippuric acid to yield 5-keto-2-phenyl-4-(4′-benzyloxy-3′-methoxybenzylidene)-4,5-dihydroöxazole. The latter then was hydrolyzed with barium hydroxide to give 3-methoxy-4-benzyloxyphenyl-pyruvic acid, which was readily oxidized with hydrogen peroxide to provide the desired 3-methoxy-4-benzyloxyphenylacetic acid, m.p. 114–116° [lit. (2) m.p. 116°]. This acid was converted to its acid chloride with thionyl chloride prior to reaction with β-methoxy-β-(3-benzyloxy-4-methoxyphenyl)ethylamine, which was obtained by treating the nitromethane adduct of *O*-benzylisovanillin with sodium methoxide, according to Rosenmund *et al.* (3), to give 1-methoxy-1-(3-benzyloxy-4-methoxyphenyl)-2-nitroethane,[1] m.p. 100–102°, which was then reduced with lithium aluminum hydride. The resulting amide, m.p. 96.5–98.5°, was then submitted to Bischler–Napieralski cyclization (4) with phosphorus oxychloride to give 1-(3′-methoxy-4′-benzyloxybenzyl)-6-benzyloxy-7-methoxyisoquinoline, m.p. 146–147°.

Another route to this isoquinoline was achieved by dehydrogenation of the known 1-(3′-methoxy-4′-benzyloxybenzyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (5) with 10% palladium-on-carbon and rebenzylation of the resulting phenolic isoquinoline with benzyl chloride according to Lee and Soine (6). This route also served to confirm the identity of the isoquinoline from the first method. The tetrahydroisoquinoline was prepared, according to Tomita and Kunimoto (5), by condensation of 3-methoxy-4-benzyloxyphenylacetyl chloride with β-(3-benzyloxy-4-methoxyphenyl)-ethylamine. Subsequent Bischler–Napieralski cyclization with phosphorus pentachloride gave 1-(3′-methoxy-4′-benzyloxybenzyl)-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline hydrochloride. The latter, on reduction with sodium borohydride in aqueous methanol, provided the desired tetrahydroisoquinoline.

The isoquinoline obtained by either of the two methods then was quaternized with methyl iodide and reduced with sodium borohydride in pyridine, according to Barton *et al.* (7), to yield 1-(3′-methoxy-4′-benzyloxybenzyl)-2-methyl-6-benzyloxy-7-methoxy-1,2-dihydroisoquinoline, m.p. 61–64°. Acid cyclization of this product, by the method of Battersby and Binks (8), gave (±)-bisnorargemonine, m.p. 231.5–232.5°. Except for melting point and rotational differences, the natural and synthetic compounds were shown to be identical. The identity of natural and synthetic materials was established by comparative UV, IR, NMR, and mass

[1] This compound has been prepared but not described by E. Brochmann-Hanssen and K. Hirai, *J. Pharm. Sci.*, **57**, 940(1968). Private communication with the authors indicates that the compound was obtained as a pale-yellow oil with suitable chromatographic and NMR characteristics. Our solid product meets similar criteria and is assumed to be identical to their product.

spectral analyses. Such criteria left no doubt that the original structural assignment (1) was correct.

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Improved Method for Measuring Output Potential of Specific Ion Electrodes

Keyphrases □ Ion electrodes, specific—output potential measurement □ pH meter, expanded scale—ion electrode potential output determination

Sir:

Since Frant and Ross (1) announced the invention of a single crystal lanthanum fluoride electrode for the determination of fluoride-ion activity, numerous articles have appeared in the literature describing applications of the device. It has been used to determine fluoride in bone (2), urine (3), chromium plating baths (4), tungsten (5), toothpaste (6), and numerous other samples.

In these methods, either an expanded scale analog or digital pH meter was used to measure fluoride-ion activity electrode potential. When using an expanded scale pH meter, it is possible to read electrode potentials to about ±1 mv. According to the report of Lingane (7), this would represent an error of ±0.017 pF unit, or a relative accuracy of ±1.7%. With a digital pH meter, it is possible to measure potentials to ±0.1 mv., with a correspondingly greater relative accuracy.

When determining the fluoride content of some pharmaceutical preparations without a digital pH meter, it was necessary in the authors' laboratory to devise a method of measuring the electrode potential more accurately than can be done directly with an expanded scale analog instrument. This was accomplished by using an expanded scale pH meter as an electrometer coupling between the electrode and a variable range strip-chart recorder, which involves simply connecting the recorder into the appropriate electrical output jacks of the meter. By so doing, and by choosing the proper input range of the recorder, it is possible to expand almost any portion of a standard curve [*i.e.*, almost any millivolt range of the plot: log (concentration F^-) *versus* millivolts] to full-scale deflection on the chart.

The most convenient way is to operate the pH meter in the pH (expanded scale) mode. This is done to keep the calibration circuit of the meter activated.

For the present work, a Corning model 10 expanded scale pH meter was used. While some of its characteristics (*i.e.*, deactivation of the calibration circuit when operated in the millivolt mode) may not be common, simple modifications of this procedure should make it applicable to individual needs.

After choosing the desired concentration range for the standard curve, the fluoride and reference electrodes are placed in the least concentrated standard sample. The calibration knob of the pH meter is then adjusted to bring the recorder pen to zero. Thus, at this concentration, the recorder will sense a zero potential from the electrode. The electrodes are then placed in the most concentrated standard, and the span control of the recorder is adjusted to bring the pen to fullscale deflection. To do this, the span control of the recorder must be infinitely variable between any two coarse span settings. One or two standards of intermediate concentrations are then used, and the pen deflection is noted.

When this is done, the numbers read from the chart become arbitrary units, not millivolts. However, the relationship, log (concentration F^-) *versus* recorder reading, is still linear. The concentration range is chosen on the basis of a compromise between a range narrow enough to allow sufficient accuracy and one wide enough to suppress electronic noise from the electrode. In the authors' laboratory, a three or fourfold concentration range was found reasonable. This range requires the recorder to have a fullscale deflection of about 1.5 mv.

In addition to a high degree of accuracy, several advantages are realized with the use of the recorder:

1. It provides a superb method of determining when the electrodes reach equilibrium; one need only note the point at which the needle ceases to drift. In extremely dilute solutions, equilibration time may be 30–45 min.

2. As reported by Strinivasan and Rechnitz (8), the electrode was found to drift, necessitating frequent recalibration. Because the slope of the calibration curve did not change, recalibration could be accomplished in a few minutes by adjusting the reading of one of the standard solutions to its original value on the recorder with the calibration knob of the pH meter.

3. The recorder gives a graphic presentation of the electronic noise produced by the electrode. This can be significant when the recorder is operated in the 1–2 mv. range. With the recorder, one can read potentials in spite of noise.

While work using this procedure in the authors' laboratory was conducted with a fluoride electrode, the