crease in duration relative to the hydrochloride salt, more clearly at 40.0 than at 4.0 mg/kg. The zinc tannate complex in peanut oil showed at least a threefold prolongation of the activity of the hydrochloride, and there was a further roughly threefold prolongation of activity when the zinc tannate was incorporated in the aluminum monostearate gel. Indeed, naltrexone zinc tannate in the gel medium still evidenced 70% antagonism 19 days after injection of the 40.0-mg/kg dose. The mice showed no behavioral or other adverse drug effects even at the 40-mg/kg dose.

This work is continuing. We earlier speculated as to the nature of the zinc tannate complexes (8) and indicated that the metal ion appeared to bond covalently to the same sites as were involved in ionic bonding with drug since the zinc displaced an equivalent amount of drug from the complex and the equivalents ratios remained substantially constant. We recently found[7] that by varying the method of preparation, we can increase the amount of zinc in the complex without further reducing the amount of drug. The resultant complexes show reduced percent dissociation *in vitro* and increased duration of activity *in vivo*. We also prepared analogous complexes containing aluminum in place of zinc which show somewhat enhanced duration of activity.

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[7] Unpublished data.

Conversion of Apocodeine to Apomorphine and Norapomorphine in Rats

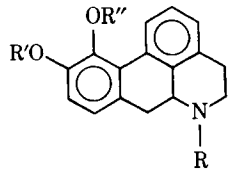
Keyphrases □ Apocodeine—metabolic conversion to apomorphine and norapomorphine, rats □ Apomorphine and norapomorphine—urinary metabolites of apocodeine, rats □ Norapomorphine and apomorphine—urinary metabolites of apocodeine, rats

Sir:

There is renewed and increased interest in the biological activities of aporphine compounds. This has resulted in part from the finding that apomorphine (I) has some usefulness in the treatment of Parkinson's disease (1–8). Apocodeine (II) is an important homolog of I. The relatively poor dopaminergic activity of II (and III) in pigeons and dogs (9, 10) led Cannon *et al.* (10) to theorize that both phenolic groups of I are required to exert central emetic effects. Recently, however, Lal *et al.* (11) reported that II induced stereotyped behavior and caused reversal of reserpine-induced catalepsy in rats similar to that of I. While its activity is described as intermittent, II is clearly one-fourth as active as I (11). Lal *et al.* (11) suggested that these latter observations might be explained by *in vivo* conversion of II to I. Our recent experiments show that I and norapomorphine (IV) are metabolites of II in rats.

Male Sprague–Dawley[1] rats (175–300 g) were injected with II-HCl (30 mg/kg ip); urine, separate from feces, was collected for 48 hr following injections and frozen. The first and second 24-hr samples (4–12 ml) were made up to 12 ml with distilled water; 3 ml of 3 *N* hydrochloric acid was added to each, and the mixtures were heated at 100° for 1 hr. The hydrolysates were adjusted to pH 7.0 with 1 *N* sodium hydroxide and extracted with three 10-ml portions of ethyl acetate. The separators were rinsed with 10 ml of ethyl acetate and the combined extracts were reduced to dryness *in vacuo;* the residues were dissolved in 1–2 ml of acetone for TLC analysis.

Sample and blank urine extracts were spotted on silica gel GF_{254} plates[2] (250 μm) and then developed in the following solvent systems: 1, chloroform–methanol (85:15); 2, acetone; and 3, acetone–methanol (1:1). Detection was *via* quenching of 254 nm-induced fluorescence and visualization of plates allowed to stand in the air for 12–24 hr. Authentic I[3]



I: R = CH_3; R′, R″ = H
II: R, R′ = CH_3; R″ = H
III: R, R′, R″ = CH_3
IV: R, R′, R″ = H

[1] Sprague–Dawley Co., Madison, Wis.
[2] Analtech, Newark, Del.
[3] S. B. Penick, New York, N.Y.

Table I—TLC Mobilities of Authentic Apomorphine and Norapomorphine and Urinary Apocodeine Metabolites

TLC System	$R_f \times 10^2$		
	Authentic		
	Apomorphine	Norapomorphine	Apocodeine Metabolites[a]
Chloroform–methanol (85:15)	33	8	32, 8
Acetone	40	8	40, 8
Acetone–methanol (1:1)	68	43	68, 43

[a] Identified in 12 separate experiments with 12 animals.

Table II—Conversion of Apocodeine to Apomorphine and Norapomorphine in Rats

Metabolite	Percent Conversion[a]	
	Range[b]	Mean
Apomorphine	8.1–11.0	9.6
Norapomorphine	15.8–18.4	17.2
Totals	23.9–29.4	26.8

[a] From separate analyses of 24-hr urines of three rats. [b] Data were corrected for losses due to extraction (13); losses due to hydrolysis were: I, 18% (five experiments); and II, 9% (two experiments).

and IV [prepared according to the literature procedure (9)] yielded blue-green-colored spots, presumably due to formation of *ortho*-quinone-type oxidation products (12). Quantitation of I and IV was by TLC fluorescence quenching (13).

TLC examination of extracts of hydrolyzed urine[4] obtained from animals injected with II-HCl revealed the presence of I and IV (Table I). In addition, these metabolites seemed to be entirely excreted (as their conjugates) during the first 24 hr following injection. Quantitative evaluation of these results gave the data indicated in Table II. Compound II shows about one-fourth the central nervous system activity of I in rats (11), and one-quarter of the dose of II appears to be converted to I and IV. Although the ability of IV to induce stereotyped behavior and reverse reserpine-induced catalepsy in rats does not seem to have been evaluated, the structural similarities of I and IV suggest that IV might have significant activity. This suggestion is somewhat contradicted by the apparent low order of activity of IV causing compulsive gnawing in mice (9).

The observations reported here support the suggestion (11) that the pharmacological activities of II in the rat may be due to its conversion to I and/or IV. The *in vivo* formation of I and IV from II also has interesting and important implications with respect to the design of apomorphine prodrugs and the mechanism of action of I and a number of its analogs.

[4] During preliminary experiments, no free I and IV were detected, as indicated from TLC analysis of ethyl acetate extracts of unhydrolyzed urine.

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