Since the sign of a Cotton effect is governed chiefly by the stereochemical environment of the responsible optically active chromophore (Crabbé & others, 1965), the identity of sign noted for Cotton effects in (−)-I and (−)-II provides strong evidence for the configurations of the C-9, 13 and 14 asymmetric centres of (−)-morphine being the same as those of the corresponding centres of levorphanol. Portoghese (1966, quoting unpublished data) reports that the o.r.d. curves of some (−)-phenolic benzomorphan derivatives exhibit Cotton effects which also have the same sign as that of morphine. Hence, the results of o.r.d. studies substantiate previous conclusions of configuration based upon work involving stereoselective adsorbents (Beckett & Anderson, 1960).

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Note added in proof. Weiss & Rull (1965) report Cotton effects (by circular dichroism measurements) of similar sign near 260μ) for (—)-3-methoxy-*N*-methylmorphinan, dihydrodesoxycodeine and tetrahydrodesoxycodeine, results which provide further evidence of configuration in morphinan derivatives.

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Excretion of a glucuronide conjugate of 3-hydroxyphenyltrimethylammonium

SIR,—We have found that, after intramuscular injection of neostigmine in the rat, about 50% of the dose is excreted in the urine unchanged, a high proportion of the remainder being metabolized in the liver and excreted in the urine as 3-hydroxyphenyltrimethylammonium (Roberts, Thomas & Wilson, 1963, 1965a,b). We anticipated that some of this phenolic metabolite might be excreted as a conjugated product (described by Williams, 1959), but the paper electrophoresis technique we used did not enable us to establish this point.

Further investigation using [^{14}C]3-hydroxyphenyltrimethylammonium by intramuscular injection into rats showed that when the urine was examined by a modification of the electrophoresis procedure (Veronal buffer pH 7·0, 0·05M), two peaks of radioactivity were obtained. One of these peaks corresponded with a concurrently run authentic sample of 3-hydroxyphenyltrimethylammonium, the other was tentatively assumed to be the glucuronide conjugate of this compound. This assumption was confirmed by incubating samples of urine with β-glucuronidase ("Ketodase", Warner & Co.) and when these were subjected to paper electrophoresis, only the peak for 3-hydroxyphenyltrimethylammonium was identified.

Using this procedure urine was collected from rats for periods up to 24 hr after intramuscular injection of [^{14}C]3-hydroxyphenyltrimethylammonium. Fig. 1

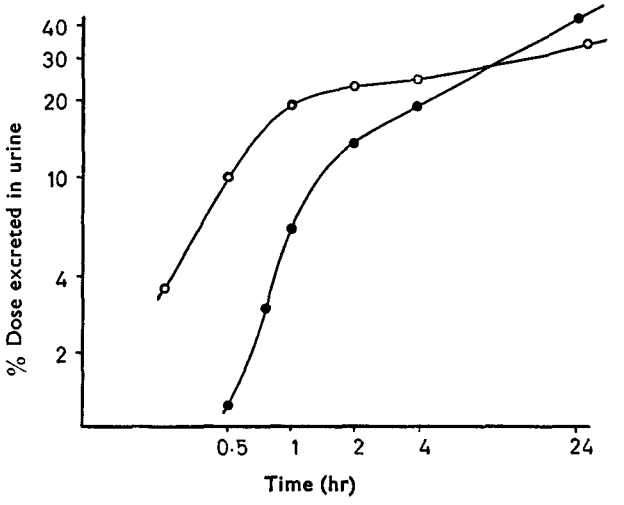

FIG. 1. Excretion in rat urine of 3-hydroxyphenyltrimethylammonium (○——○) and its glucuronide conjugate (●——●) after intramuscular injection of 100 μg of [^{14}C]3-hydroxyphenyltrimethylammonium. Each point is the mean of 3 experiments.

shows that more than half the dose was excreted as the glucuronide in 24 hr. Additional experiments using [^{14}C]neostigmine by intramuscular injection have shown that during 24 hr approximately 50% of the phenolic metabolite is excreted as the glucuronide conjugate.

The relevance of this mechanism for the metabolism and excretion of neostigmine by patients with myasthenia gravis is currently under investigation.

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The *N*-oxidation of chlorpromazine *in vitro*—the major metabolic route using rat liver microsomes

SIR,—Incubation of chlorpromazine with suitably fortified liver homogenates has been shown to result in sulphoxidation (Salzmann & Brodie, 1956; Gillette & Kamm, 1960), demethylation (Young, Ross & Maass, 1959; Ross, Flanagan & Maass, 1962), and hydroxylation (Robinson & Beaven, 1964) of the drug molecule.

Recently (Curry, 1965; Robinson, 1966), attempts were made to obtain a comprehensive picture of *in vitro* chlorpromazine metabolism after incubation