TABLE I—ANALGESIC POTENCY OF PRODINE ENANTIOMERS

Compound	ED_{50}[a], mg./Kg.
dl-α-Prodine HCl	1.7
(+)-α-Prodine HCl	0.90
(−)-α-Prodine HCl	22.0
dl-β-Prodine HCl	0.35
(+)-β-Prodine HCl	0.25
(−)-β-Prodine HCl	2.6
3-Desmethylprodine HCl	1.3
Meperidine HCl	12.0

[a] Analgesic activity was determined by a modified hot plate method (13).

method, it is very probable that Ib was only partially resolved.

It is significant that the C-3 asymmetric centers in the more potent isomers have opposite configurations. This, coupled with the observation that desmethylprodine (9) possesses greater potency than either of the less active prodine isomers (Table I) suggests that the 3-methyl group does not contribute to the drug-receptor interaction in a totally positive fashion. The difference in potency between (+)-Ia and (+)-Ib most probably is related to different brain levels[1] and it is conceivable that the lower potency of desmethylprodine, when compared to the more active antipodes, may largely be due to lower brain levels rather than to the absence of involvement of the 3-methyl group at the receptor level.

It is noteworthy that the more active enantiomers of isomethadone (VII) (10) and Ia are configurationally related (11). Since the desmethyl analog (VIII) (12) possesses potency which is comparable to VII, there exists the possibility that in this case the methyl group of (*S*)-isomethadone is also playing primarily a passive role in the interaction with analgesic receptors.

[1] Preliminary experiments indicate that the brain levels of β-prodine in rats are greater than those of the α-isomer and that this is the primary factor determining the potency difference between these diastereomers.

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Keyphrases

Prodine enantiomers—absolute sterochemistry
Optical rotation—structure
IR spectrophotometry—structure
NMR spectroscopy—structure
ED_{50}—prodine enantiomers
Absolute configuration—analgesic activity

4,4′-Dihydroxybibenzyl, a Reduction Metabolite of *trans*-Stilbene

Sir:

Our investigations of the metabolism of certain stilbenes has revealed a unique conversion of *trans*-stilbene in rabbits (2.1%)[1] to 4,4′-dihydroxybibenzyl.

The above metabolite (originally designated X) was found in a phenolic fraction obtained from an ether extract of urine of rabbits, which had been administered *trans*-stilbene (25 mg./Kg., i.m.). Paper, thin-layer, and vapor phase chromatography (VPC) (1) of this phenolic fraction disclosed the presence of the *trans*-stilbenes, 4-hydroxy-, 4,4′-dihydroxy-, 3-hydroxy-4-methoxy-, and 4-hydroxy-3-methoxystilbene, and X, which was not comparable to these or other simple phenolic stilbenes. A 2-mg. sample of the trimethylsilyl (TMS) either of X, obtained by preparative VPC, was subjected to IR, UV, and mass spectral analysis.

The IR spectrum of the TMS derivative of X,

[1] Determined by VPC (TMS ether). Chromatographic analysis of urine obtained from guinea pigs administered *trans*-stilbene has indicated an even greater (10.6%) conversion to 4,4′-dihydroxybibenzyl.

except for differences in the fingerprint region, was similar to that of reference 4-trimethylsiloxy- and 4,4′-di(trimethylsiloxy)stilbene. The UV spectrum, however, with a single $\lambda_{max.}$ at 280 mμ, was atypical for the *trans*-stilbene chromophore (2). Mass spectral analysis[2] of the isolated derivative showed a weak parent peak at m/e = 358, a base peak at m/e = 179, and other prominent peaks at m/e = 286 and m/e = 107.

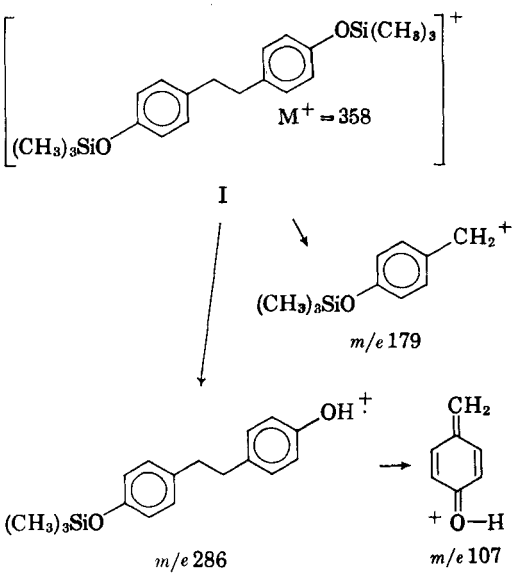
With these data, structure I was proposed for the TMS derivative of X and its mass spectral breakdown was rationalized as in Scheme I.

Based upon this determined molecular weight of 358, a molar absorptivity of 3460 (at 280 mμ) was calculated for the TMS derivative of X and this provided additional evidence for the proposed structure (3).

The TMS derivative of X was found to co-chromatograph (VPC) with the di-TMS ether of authentic 4,4′-dihydroxybibenzyl. Hydrolysis of the isolated TMS derivative of X and comparison of the product (X) with 4,4′-dihydroxybibenzyl showed complete agreement in mobility and reaction to diazotized sulfanilic acid in three thin-layer systems and further substantiated the identity of X as 4,4′-dihydroxybibenzyl.

The formation of a bibenzyl derivative, a reduction product from *trans*-stilbene, involves a novel metabolic transformation for this class of compounds. In contrast, metabolic schemes incorporating reductions are well established for nitro- and azo-compounds, including the reduction of the stilbene isostere, azobenzene to hydrazobenzene (4), a postulated intermediate in the reductive cleavage of azobenzene (5). Reports of metabolic reductions of carbon-carbon double bonds are primarily limited to Δ^4-3-keto-steroids (6, 7) and certain cinnamic acid derivatives (8). These reductions are analogous to the well-known hydrogenations of α,β-unsaturated carbonyl compounds which occur in intermediary metabolism. Reductions resembling the one found in the present investigation, however, are rare and in combination with the implied reductive step in the formation of 1,2-dihydronaphthols (9), advance the significance of hydrogenation in the metabolism of similar conjugated ethylenic compounds.

[2] The authors are indebted to Luther H. Smithson, Jr., and Rick Faubert of Varian Associates, Palo Alto, Calif., for the mass spectral data.



Scheme I

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Keyphrases

trans-Stilbene—conversion in rabbits
4,4′-Dihydroxybibenzyl—urinary metabolite *trans*-stilbene
Vapor phase chromatography—identity
TLC—identity
IR spectrophotometry—identity
UV spectrophotometry—identity
Mass spectroscopy—structure