Absolute Configuration and Psychotomimetic Activity

George M. Anderson, III, Gisela Braun, Ulrich Braun, David E. Nichols, and Alexander T. Shulgin

Most of the known psychotomimetic agents have at least one chiral center within their structures but have been studied only as the racemic mixtures. All of those which have been studied in optically active form are consistent in that the more potent isomer is the isomer with the absolute "R" configuration at the chiral center carrying the nitrogen that corresponds to the amino group of the phenethylamine moiety. With LSD, the 5-"R", 8-"R" isomer is effective in man within the dosage range of 0.05-0.1 mg, whereas the diastereo-isomeric 1-iso-LSD (5-"S", 8-"R") is inactive in man at twenty times this dosage (Hofmann 1959). Four of the ring-substituted phenylisopropylamine psychotomimetics have been studied in their optically active forms. With 4-bromo-2,5-dimethoxyphenylisopropylamine (DOB) the "R" isomer is effective at 0.5 mg, approximately twice the potency of the racemate (Shulgin et al. 1971), whereas the "S" isomer is only about a fifth as potent. The "R" isomer of 4-methyl-2,5-dimethoxyphenylisopropylamine (DOM, STP) is reported as being at least four times more potent as a psychotomimetic than the "S" isomer (Shulgin 1973). These observations with both DOB and DOM are parallel to those observed in biochemical studies (Dyer et al. 1973) and in animal models (Benington et al. 1973), although these latter studies were conducted at nearly lethal dosages. The ethyl homolog of DOM, 4-ethyl-2,5-dimethoxyphenylisopropylamine (DOET), has been studied as its optical isomers (Snyder et al. 1974) and here again the "R" isomer is approximately four times the activity of the "S" counterpart. Finally, the "R" isomer of 3,4-methylenedioxyphenylisopropylamine (MDA) is reported to be three-fold more potent than its optical enantiomer (Marquardt 1978).

Amphetamine itself, on the other hand, is at nominal dosages a stimulant rather than a psychotomimetic drug. In direct comparisons of its optical isomers in man, it
is the "S" or dextrorotatory form that is the more active. In most titration measurements in clinical studies it is accepted as being about twice as potent as the "R" isomer (Smith and Davis 1977), although the levo, or "R", isomer has been reported to be as effective as the "S" isomer in the development of a psychotic syndrome (Angrist et al. 1971). These comparisons are presented in table I.

### TABLE I
RELATIVE POTENCIES OF THE OPTICAL ISOMERS OF SEVERAL CNS AGENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>CNS Action</th>
<th>Chiral carbon</th>
<th>Potency Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSD</td>
<td>Psychotomimetic</td>
<td>5  R &gt; S</td>
<td>&gt;x20</td>
</tr>
<tr>
<td>DOB</td>
<td>Psychotomimetic</td>
<td>5  R &gt; S</td>
<td>x10</td>
</tr>
<tr>
<td>DOM</td>
<td>Psychotomimetic</td>
<td>5  R &gt; S</td>
<td>x4</td>
</tr>
<tr>
<td>DOET</td>
<td>Psychotomimetic</td>
<td>5  R &gt; S</td>
<td>x4</td>
</tr>
<tr>
<td>MDA</td>
<td>Psychotomimetic</td>
<td>5  R &gt; S</td>
<td>x2</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Stimulant</td>
<td>5  R &gt; S</td>
<td></td>
</tr>
</tbody>
</table>

Several other clinically used CNS stimulants contain the same chiral center as does amphetamine but they have been studied in man only as the "S" form (as with phenmetrazine) or in the racemic form (as with fenfluramine, mephentermine, methylphenidate and fenethylline). There are no reports with these drugs of the "R" isomer having been evaluated in man.

In addition to optical properties, there is another structural feature that can be employed to separate the various phenethylamine-type psychotomimetics into two groups, i.e., the effect on the potency of the drug with methylation of the primary amino group. Six pairs of homologs have been studied and can be compared as to their psychotogenic potency. Four of these compound pairs (all trisubstituted on the aromatic ring) show a drop of from a half to a whole order of magnitude upon N-methylation. Two of these, DOB and DOM, upon N-methylation are less effective as psychotomimetic agents by a factor of ten. The other two, 3,4,5-trimethoxyphenylisopropylamine and the 2,4,5-counterpart (TMA and TMA-2, respectively), are decreased in potency by a factor of three. The remaining psychotomimetic, MDA, is unique in that upon N-methylation, it maintains substantially an unchanged potency (Shulgin and Nichols 1978) although undergoing subtle changes in the qualitative nature of the induced intoxication. The drug amphetamine, although a stimulant at normal clinical dosages, can exhibit dramatic psychotomimetic properties when used chronically. The N-methyl homolog methamphetamine is similarly psychotoxic and thus these represent a pair of compounds resembling in this respect MDA but being
quite dissimilar from the other phenethylamine psychotomimetics. These relationships are summarized in table II.

**TABLE II**

**RELATIVE POTENCIES OF SEVERAL PRIMARY AMINES AND THEIR N-METHYL HOMOLOGS AS PSYCHOTOMIMETIC AGENTS**

<table>
<thead>
<tr>
<th>Parent NH₂ drug</th>
<th>Relative potencies NH₂ vs. NHCH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>dl-DOB</td>
<td>×10</td>
</tr>
<tr>
<td>dl-DOM</td>
<td>×10</td>
</tr>
<tr>
<td>dl-TMA</td>
<td>&gt;×3</td>
</tr>
<tr>
<td>dl-TMA-2</td>
<td>&gt;×3</td>
</tr>
<tr>
<td>dl-MDA</td>
<td>=</td>
</tr>
<tr>
<td>d-Amphetamine</td>
<td>=</td>
</tr>
</tbody>
</table>

It is apparent that the N-methyl homolog of MDA, N-methyl 3,4-methylenedioxyphenylisopropylamine or MDMA, might be a drug with unusual properties. Its parent, MDA, is a drug with the expected absolute configuration for psychotomimetic activity, but it is unlike the other psychotomimetics in that it does not suffer a diminution of potency upon N-methylation.

This report discusses the comparative pharmacology and psychopharmacology of MDMA which has been prepared in the form of its optical isomers. The two bases "R" (-) MDMA and "S" (+) MDMA were prepared synthetically as shown (for the "R" isomer) in the scheme:

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3,4ace-Methylenedioxybenzyl methyl ketone (piperonylacetone) was coupled with (-) "R" benzylmethylamine, and the resulting Schiff base reduced with Raney nickel. Catalytic reduction of this "R,R" secondary base pro-viaea "R"-MDA, (a)D= -24.7, agreeing in physical and chromatographic properties with a sample obtained from NIDA, Rockville, Maryland. This base was formylated in methyl formate in a sealed tube and the resulting forma-```
mide had a reversed rotation (α)D= +12.4 (in ethanol) and m.p.= 99-101. Reduction of this amide in THF with LAH provided the desired "R"-MDMA, (α)D= -18.2, m.p.= 181-183 as the HCl salt. The "S" isomer was prepared in an exactly parallel manner, with the primary amine showing (α)D= +25.3, the amide (α)D= -12.6, m.p.= 101-102, and the final "S"-MDMA with (α)D= +17.2 and a m.p.= 184-185. Racemic MDMA m.p.= 150-151.

An evaluation of the two optically active isomers, in comparison with the racemic form of MDMA, was made in rabbits, using the evoked rectal hyperthermia as a measure of central activity. The literature procedure (Aldous et al. 1974) was followed, and the two methods suggested for the evaluation of potency were employed: Method A utilized the mean maximum temperature rise (determined by a plot of ΔT vs. log dose), Method B employed an integration of the temperature-time curve as a measure of effectiveness. All compounds were assayed in at least three doses, in duplicate animals, and all values were normalized against racemic DOM, which was given the arbitrary value of 100. The results for MDMA in its optically active form and as the racemate are given in table III. The values obtained for MDA are presented for purposes of comparison.

| TABLE III |
| RABBIT HYPERTHERMIA, RELATIVE POTENCY OF TEST COMPOUNDS, WITH dl-DOM = 100 |

<table>
<thead>
<tr>
<th>Compound</th>
<th>Method A (Mean Maximum)</th>
<th>Method B (Integral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dl-MDMA</td>
<td>1.96</td>
<td>1.15</td>
</tr>
<tr>
<td>&quot;R&quot;-MDMA</td>
<td>0.71</td>
<td>~0.5*</td>
</tr>
<tr>
<td>&quot;S&quot;-MDMA</td>
<td>4.81</td>
<td>1.30</td>
</tr>
<tr>
<td>dl-MDA</td>
<td>2.46</td>
<td>1.51</td>
</tr>
<tr>
<td>&quot;R&quot;-MDA</td>
<td>3.48</td>
<td>2.29</td>
</tr>
<tr>
<td>&quot;S&quot;-MDA</td>
<td>2.93</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*Assays were conducted near the LD50, and several animals were lost during the experiment.

Two features are immediately apparent from table III, both of which are in exact accord with the human intoxication aspects which will be discussed below. First, it is apparent, employing either method of evaluation, that MDMA is about two orders of magnitude less potent than the reference compound DOM and that it is slightly less potent than the N-desmethyl homolog MDA. Second, although it is clearly apparent that the "R" isomer of MDA is more effective than the "S" isomer with either method of calculation, with MDMA this poten-
cy assignment is reversed. "S"-MDMA is more effective as a CNS agent than is "R"-MDMA. Less apparent from the table, but a point to be brought out during the discussion below concerning human clinical evaluation, is the disconcerting absense of additivity between the component isomers in comparison with the activity of the racemate.

The three chemical species racemic MDMA, "R"-MDMA and "S"-MDMA, were evaluated in normal human subjects as their hydrochloride salts, orally, by established procedures (Shulgin et al. 1969). A plot of the quantitative response factor (judged as any of five points, −,±,+;++ , and +++ , depending upon the degree and the disruptiveness of the induced intoxication) against dosage, for each of the three chemical species, is shown in figure I. All responses at a given dose for a given compound are averaged and plotted as a single data point.

FIGURE I
HUMAN RESPONSE TO "R", "S" AND dl-MDMA

The data in figure I represent 35 clinical trials. The effective dosage for racemic MDMA has been presented as being in the range 75-150 mg (Shulgin and Nichols 1978) and 100-160 mg (Shulgin et al.1978). Both values range in complete accord with the response of ++ being representative of a nominal intoxication as seen in the figure. The "S" isomer is more active than its optical enantiomorph, being effective within the dosage range of 80-120 mg. This range, however, is a larger dosage than is calculated (50-80 mg) by halving the racemate. As the contribution of the "R" isomer is little if any at
these levels, it must be concluded that the racemate is more effective as a CNS agent than would be expected or calculated from the separate activities of the component optical isomers. No acceptable value for the effective dose of the "R" isomer is clear from these data, but it would-appear that an effective dose might lie in the vicinity of 300 mg. Qualitatively, most of the sensory and interpretative properties reported for the racemate are seen in the "S" isomer, including the frequent physical toxicity manifestations of mydriasis and jaw-clenching. The "R" isomer is free of both side effects, even at the highest doses assayed. However, two subjects who experienced color enhancement on the racemate observed this peculiarity only with the (otherwise ineffective) "R" isomer. It must be concluded, within the data presently in hand, that with this one psychotomimetic compound, MDMA, the active optical isomer is the absolute "S" isomer with the configuration of dextro-amphetamine, in contrast with the previous generality that the activity of racemic psychotomimetic compounds could be largely accounted for by the "R" isomer.

The inability of the component isomers to adequately account for the action of the racemate is unusual but not without precedent with similar compounds in the literature. There are numerous reports where there is a clear interaction between the component isomers of racemic compounds in in vitro studies; this is well established in the metabolism of both amphetamine (Gal et al. 1976) and DOM (McGraw et al. 1977). In vivo studies in animals with 3,4-dimethoxyphenylisopropylamine (3,4-DMA) (Barfknecht and Nichols 1972) showed that the "R" isomer was only a third as active as the "S" isomer, and that neither could duplicate the characteristic effects of the racemic mixture.

The purpose of this report is not to explain or theorize on the persistence of activity following the N-methylation of MDA or on the unexpected reversal of activity assignment to the optical isomers. It is, rather, to present these findings and to let them provoke the necessary changes in receptor-site theory that must be made. Since the effects of MDA to some extent, and of MDMA to a very large extent, are far removed from that constellation of symptoms usually associated with psychotomimetic drugs such as TMA, DOM, and LSD, it is appealing to explain the difference of assymetric requirements in accord with these differences in qualitative responses, and to conclude that there is some different receptor site being acted upon in this case. There is no insistence that all psychotomimetic agents act by a single mechanism. It has been proposed (Cheng et al. 1974) that hallucinogenic drugs might be usefully classified either as direct acting or as indirect acting releasing agents. Most psychotomimetics appear to act
as direct serotonin agonists, but materials such as
para-methoxyphenylisopropylamine (PMA) and MDA do not
fit this model quantitatively (Nichols et al. 1977).
Although no human studies have been conducted with the
isomers of PMA, both PMA and MDA have been demonstrated
to be indirect acting sympathomimetics (Nichols et al.
1974; Paton et al. 1975).

MDMA probably does not act by demethylation, as the
reversal of optical requirements speaks against such a
mechanism. This is further supported by the absense of
cross-tolerance between these two drugs in man. Perhaps
there is a stimulant action from one of the isomers
which enhances or potentiates the (otherwise) dormant
potential of the other. Such questions can be answered
only by further experiments.

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