Resolution and Absolute Configuration of *trans*-2-(2,5-Dimethoxy-4-methylphenyl)cyclopropylamine, a Potent Hallucinogen Analogue

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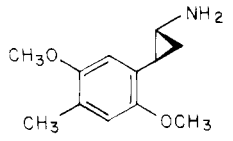
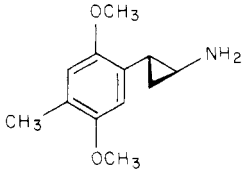
An hallucinogen analogue, *trans*-2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine (DMCPA), was resolved into its two enantiomers by fractional crystallization of salts with *d*- or *l*-*O*,*O*-dibenzoyltartaric acid. A comparison of the ORD and CD curves of the *N*-5-bromosalicylidene derivatives of *trans*-2-phenylcyclopropylamine of known absolute configuration and of the title compound established the stereochemistry of the latter to be (1*R*,2*S*)-(−) and (1*S*,2*R*)-(+). We have earlier shown that the (−) isomer shows selective behavioral effects in cats and mice. In the present study it was found that the (−) isomer selectively elicits rabbit hyperthermia when compared with the (+) isomer. In view of the stereoselective ability of the (−) isomer to elicit hallucinogen-like behavioral profiles in these animal models, the proof of absolute configuration lends further support to a new model which interrelates the active binding conformation of phenethylamine hallucinogens to that of serotonin and tryptamines.

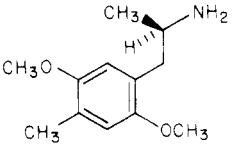
Recently, Nichols et al.[1] proposed a new model for the receptor which interrelates the structures of phenethylamine hallucinogens, LSD, and serotonin. Fundamental to the validity of this new model was the prediction that the 1*R*,2*S* isomer of *trans*-2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine (**1a**, DMCPA) would show



1a



1b



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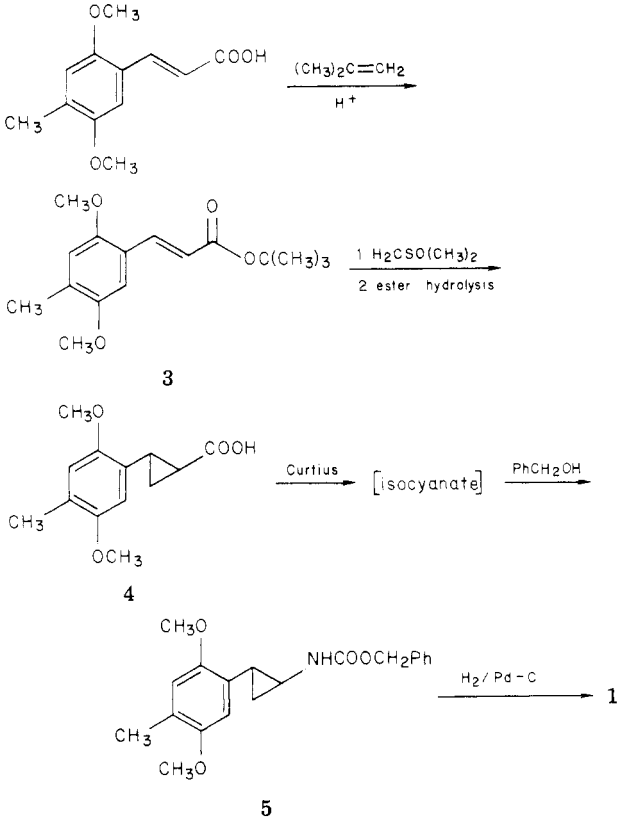
stereoselective activity when compared with the 1*S*,2*R* enantiomer **1b**. This compound has previously been reported as the racemic material by Aldous et al.[2] These workers characterized the compound as LSD-like in action and about one-third the potency of the known hallucinogen DOM (**2**). Subsequently, Nichols, Pfister, and Yim[3] reported that behavioral studies in both mice and cats showed the (−) isomer of DMCPA to be selectively active when compared with the (+) isomer. Pharmacological comparison with the optical isomers of DOM indicated DMCPA to be of the same order of potency as DOM, consistent with the report of Aldous et al.[2]

This paper describes in detail the synthesis, resolution, and determination of absolute configuration which are essential to the further development of this new receptor model. In addition, we present data for the rabbit hyperthermia model which further support stereoselectivity of action for the (−) isomer of DMCPA.

Chemistry. Racemic **1** was prepared by a modification of the method of Kaiser et al.[4] utilizing a reaction between dimethylsulfoxonium methylide and *tert*-butyl 2,5-dimethoxy-4-methylcinnamate (**3**) (Scheme I). Although it is unclear in their report, Aldous and co-workers[2] apparently used the corresponding ethyl ester for this reaction. We found the *tert*-butyl ester to give more satisfactory results, consistent with the original work by

Scheme I



Kaiser et al.[4] Hydrolysis of the resulting cyclopropane ester gave the corresponding cyclopropanecarboxylic acid **4**. The acid was subjected to the Weinstock modification of the Curtius rearrangement.[5] Treatment of the resulting isocyanate with benzyl alcohol gave the carbobenzoxamide derivative **5** in excellent yield. Hydrogenolysis of **5** over palladium on carbon led to the desired racemic amine **1**.

Chemical resolution was accomplished by recrystallization to constant rotation of the diastereomeric salts formed with either *d*- or *l*-*O*,*O*-dibenzoyltartaric acid. The resolved amines were liberated from the resolving agents and converted into their hydrochloride salts.

Attempts to obtain crystals suitable for X-ray crstallography using a variety of heavy atom containing salts or derivatives have so far proven fruitless. Since *N*-salicylidene derivatives have been reported to give excellent

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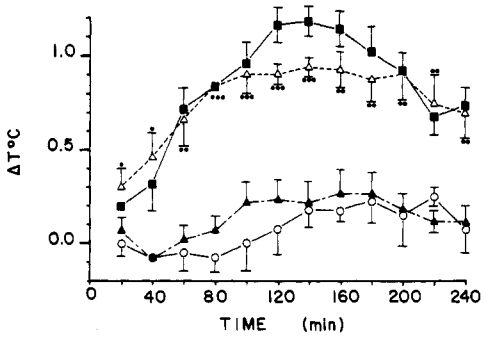

Figure 1. Rectal temperature in rabbits following iv injection of: (○) saline, $n = 4$; (■) racemic DMCPA·HCl, 1.6 mg/kg, $n = 5$; (▲) (+)-DMCPA·HCl, 0.8 mg/kg, $n = 6$; (△) (−)-DMCPA·HCl, 0.8 mg/kg, $n = 8$. The response to the (−) isomer of DMCPA was significantly different from that to the (+) isomer at all times: (●) $p < 0.05$, (●●) $p < 0.01$, (●●●) $p < 0.001$.

results in ORD studies of primary amines,[6] we therefore prepared the *N*-5-bromosalicylidene derivatives of (−)- and (+)-1. The ORD and CD curves were recorded and compared with the corresponding curves for the *N*-5-bromosalicylidene derivatives of (−)- and (+)-*trans*-2-phenylcyclopropylamine (tranylcypromine, SK & F).

Pharmacology. Recently, the ability of psychotomimetics to elicit hyperthermia in the rabbit has been correlated with potency in man.[2,7,8] We therefore examined the ability of the DMCPA isomers to elicit hyperthermia in this model. The method used is essentially that described by Aldous et al.[2] However, instead of using standard rabbit restraining boxes, we found that the use of canvas holders as described by Knize et al.[9] was more satisfactory. Since Aldous et al.[2] had compared racemic DMCPA to other hallucinogens in several animal models, we did not feel that further detailed qualitative comparisons were warranted. A dose of 1.6 mg/kg of racemic DMCPA·HCl was selected based on the data given by Aldous et al.[2] The isomers were administered at half this dose.

Results and Discussion

A comparison of the ORD and CD curves of the *N*-5-bromosalicylidene derivatives of (−)- and (+)-1 with the corresponding curves of the *N*-5-bromosalicylidene derivatives of the known (1*R*,2*S*)-(−)- and (1*S*,2*R*)-(+)-*trans*-2-phenylcyclopropylamine[10] establishes the absolute configuration of (−)-1 to be 1*R*,2*S* and (+)-1 to be 1*S*,2*R* (**1a** and **1b**, respectively). The ORD data for the *N*-5-bromosalicylidene derivatives of (−)-**1a** and (1*R*,2*S*)-(−)-tranylcypromine are given under the Experimental Section.

The results of the rabbit hyperthermia study are presented in Figure 1. The (+) isomer of DMCPA·HCl at 0.8 mg/kg did not differ significantly from saline-injected controls at any time during the experiment. On the other hand, (−)-DMCPA·HCl at 0.8 mg/kg did not differ significantly from 1.6 mg/kg of the racemate at any time and was significantly different from the (+) isomer throughout the study. These results clearly support the stereoselective nature of the response which is elicited by the (−) isomer of DMCPA and are in agreement with the data which we previously obtained in the cat and mouse.[3] Although not shown here, racemic DOM·HCl gave approximately comparable responses when administered at the same dose.

The results confirm our original prediction[1] that the 1*R*,2*S* isomer of *trans*-2-phenylcyclopropylamine analogues of hallucinogens would possess selective activity. The proposed receptor model has been represented schematically as a framework model superposition of a 2,5-dioxygenated phenethylamine and a 5-oxygenated tryptamine moiety.[3]

One of the model's unique features is its ability to explain the observed stereoselective activity for the (*R*)-(−) isomer of hallucinogenic amphetamine derivatives. This idea is based on the assumption that it is the α face of LSD which binds to the receptor. Kang and Green[11] originally made this suggestion and it has received support from conformational studies, which show that the lone-pair electrons at N-6 of LSD are directed toward the α face of the molecule in both the solid state[12] and in solution.[13] Our model thus allows the α-methyl of (−)-amphetamine derivatives (e.g., **2**) or the methylene of (−)-DMCPA (**1a**) to project toward the β or nonbinding face of the molecule. In the inactive (+) enantiomers, these groups would be oriented toward the receptor and would interfere with binding of the amino group. The salient features of this receptor model have been summarized.[3]

This model obviously does not indicate a specific role for the diethylamide function of LSD, nor does it account for the possibility of multiple sites of action for hallucinogens. Indeed, the overall intoxication state may result from actions at many receptor systems.[14-17] These interactions, in turn, may be greatly influenced by portions of the molecule other than the tryptamine moiety. Partition and distribution effects are likewise known to play a large role in describing activity and cannot be accounted for by any receptor model. We have assumed that serotonin–receptor interaction constitutes a critical or "rate-determining" step in the overall mechanism of action.[18,19] On the other hand, this model may be relevant to understanding how ergot alkaloids, and possibly certain tryptamines, are able to interact with dopamine receptors.[15,20]

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 instrument and are reported in δ values (ppm) relative to an internal standard of tetramethylsilane. Low-resolution chemical-ionization (CI) mass spectra were obtained using a DuPont 21-492 mass spectrometer and isobutane as the reagent gas. Optical rotations were measured using a Perkin-Elmer Model 241 digital polarimeter. Optical rotatory dispersion curves were determined with a Cary Model 60 spectropolarimeter in 100% ethanol at 25 °C. Rotations are given below only for the highest and lowest wavelengths measured and for peaks and troughs. Circular dichroism was measured at 25 °C with a Model 6002 circular dichroism attachment, and maxima are reported in terms of molecular ellipticity.[21] Elemental analysis was performed on new compounds by the microanalysis laboratory, Chemistry Department, Purdue University, and were within ±0.4% of the calculated values.

***trans-tert*-Butyl 2,5-Dimethoxy-4-methylcinnamate (3).** A suspension of 30 g (0.135 M) of 2,5-dimethoxy-4-methylcinnamic acid[22] in 150 mL (88 g, 1.58 M) of liquid isobutylene was placed in a 500-mL Parr reaction bottle and 0.6 mL of concentrated H_2SO_4 was added dropwise, and the bottle was tightly stoppered and shaken at room temperature for 48 h. The reaction was cooled to −10 °C and vented, and the semisolid mass was transferred into 200 mL of 10% Na_2CO_3 solution. The mixture was extracted with hexane, and the organic extract was washed (H_2O) and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave the desired ester as a viscous amber oil: yield 17 g (45%); bp 134–136 °C (0.1 mm); ^{1}H NMR ($CDCl_3$) δ 1.53 [s, 9, $C(CH_3)_3$], 2.27 (s, 3, $ArCH_3$), 3.87, 3.90 (2 s, 6, $ArOCH_3$), 6.48 (d, 1, =CH, $J_{AX} = 16.9$), 6.85, 7.05 (2 s, 2, ArH), 8.06 (d, 1, =CH, $J_{AX} = 16.9$). Anal. ($C_{16}H_{22}O_4$) C, H. Acidification of the aqueous layer from above gave a 55% recovery of the unreacted cinnamic acid.

***trans*-2-(2,5-Dimethoxy-4-methylphenyl)cyclopropanecarboxylic Acid (4).** This was prepared from the ester **3** and dimethylsulfoxonium methylide following the procedure described

by Kaiser et al.[4] Hydrolysis of the resulting crude cyclopropane ester gave **4** in 53% yield. Following recrystallization from MeOH–H_2O, the acid had: mp 136 °C; ^1H NMR ($CDCl_3$) δ 1.2–2 (m, 3, CH), 2.18 (s, 3, $ArCH_3$), 2.75 (m, 1, CH), 3.78, 3.83 (2 s, 6, $ArOCH_3$), 6.45, 6.72 (2 s, 2, ArH). Anal. ($C_{13}H_{16}O_4$) C, H.

***trans*-2-(2,5-Dimethoxy-4-methylphenyl)carbobenzoxamidocyclopropane (5).** The procedure followed was that of Weinstock,[5] utilizing 5 g (21 mM) of acid **4**. Following isolation of the intermediate isocyanate as an amber oil, 5.4 g (50 mM) of dry benzyl alcohol was added and the reaction was heated on the steam bath for 6 h. Excess benzyl alcohol was removed under high vacuum. The *N*-carbobenzoxy derivative was recrystallized from EtOAc–hexane to yield 6.13 g (85%) of product: mp 107–108 °C; ^1H NMR ($CDCl_3$) δ 1.15 (m, 2, CH_2), 2.17 (s + m, 4, $ArCH_3$, CH), 2.75 (m, 1, CH), 3.75, 3.80 (2 s, 6, $ArOCH_3$), 5.17 (s, 3, OCH_2, NH), 6.43, 6.70 (2 s, 2, ArH), 7.38 (s, 5, ArH). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

***trans*-2-(2,5-Dimethoxy-4-methylphenyl)cyclopropylamine Hydrochloride (1).** A solution of 1.5 g (4.4 mM) of **5** in 120 mL of MeOH was shaken at 35 psig of H_2 with 200 mg of 10% Pd/C for 45 min. The solution was filtered (Celite) and the filtrate was acidified with 5% HCl–EtOH. The solution was evaporated to dryness and the residue was recrystallized from EtOH–Et_2O to give 0.98 g (92%) of the hydrochloride, mp 210–211 °C, lit.[2] mp 211–213 °C.

Resolution of 1. Following the procedure above, 4.5 g (13.2 mM) of **5** was subjected to hydrogenolysis over 0.5 g of 10% Pd/C at 50 psig of H_2. Following reduction, the mixture was filtered. To the filtrate was added 4.96 g (13.2 mM) of (+)-dibenzoyl-D-tartaric acid monohydrate (Aldrich). The solution was reduced to dryness, and the solid precipitate was triturated with Et_2O and filtered to yield 7.46 g (91%) of crude salt. The salt was recrystallized three times from 95% EtOH to give 1.16 g (34%) of pure diastereomeric salt: mp 176–177 °C; $[\alpha]_D$ +51.5° (*c* 0.5, MeOH). Treatment of the salt with 10% NaOH solution gave the free base which was extracted into Et_2O, the Et_2O solution was dried (K_2CO_3) and filtered, and the HCl salt was precipitated by the addition of 5% HCl–Et_2O. The HCl salt was recrystallized from *i*-PrOH–Et_2O: mp 222–224 °C; $[\alpha]_D$ −55.6° (*c* 0.3, H_2O).

The combined mother liquors enriched in the other isomer were worked up to yield the free base, which was treated with (−)-dibenzoyl-L-tartaric acid monohydrate (Aldrich). The solid product was collected by filtration and recrystallized three times from 95% EtOH to give 1.22 g (36%) of pure diastereomer: mp 176–177 °C; $[\alpha]_D$ −51.6° (*c* 0.5, MeOH). The HCl salt was prepared as above: mp 222–224 °C; $[\alpha]_D$ +55.2° (*c* 0.3, H_2O).

Preparation of *N*-5-Bromosalicylidene Derivatives. The following general procedure was used. A solution of the resolved amine (0.2 mM) and 5-bromosalicylaldehyde (0.2 mM) in 3 mL of absolute EtOH was heated to reflux for 45 min. The solvent was removed and the residue was recrystallized from MeOH to give pure products in 66–79% yields. The melting point of *N*-5-bromosalicylidene derivatives obtained from both (1*R*,2*S*)- and (1*S*,2*R*)-*trans*-2-phenylcyclopropylamine was 107.5–108.5 °C. The melting points of the *N*-5-bromosalicylidene derivatives of (1*R*,2*S*)- and (1*S*,2*R*)-*trans*-2-(2,5-dimethoxy-4-methylphenyl)-cyclopropylamine were 105.5–106 and 105–106 °C, respectively. Chemical-ionization mass spectral analysis gave MH^+ 316, 318 (1.0:0.97) and MH^+ 390, 392 (1.0:0.98) for the *N*-5-bromosalicylidene derivatives of tranylcypromine and DMCPA, respectively.

(1*R*,2*S*)-(−)-*trans*-*N*-5-Bromosalicylidene-2-phenylcyclopropylamine: $[\alpha]_D$ −443° (*c* 0.45, EtOH); ORD (*c* 0.009, EtOH); $[\phi]_{500}$ −1334, $[\phi]_{348}$ −22 259, $[\phi]_{325}$ 0, $[\phi]_{312}$ −9830, $[\phi]_{302}$ 0, $[\phi]_{290}$ −12 639.

(1*S*,2*R*)-(+)-*trans*-*N*-5-Bromosalicylidene-2-phenylcyclopropylamine: $[\alpha]_D$ +440° (*c* 0.42, EtOH); ORD (*c* 0.0084, EtOH); $[\phi]_{500}$ +1360, $[\phi]_{348}$ +24 720, $[\phi]_{325}$ 0, $[\phi]_{312}$ +7030, $[\phi]_{302}$ 0, $[\phi]_{290}$ +15 247; CD $[\theta]_{330}$ 27 917.

(1*R*,2*S*)-(−)-*trans*-*N*-5-Bromosalicylidene-2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine: $[\alpha]_D$ −413° (*c* 0.47, EtOH); ORD (*c* 0.0094, EtOH); $[\phi]_{500}$ −2050, $[\phi]_{350}$ −28 900, $[\alpha]_{332}$ 0, $[\phi]_{315}$ +43 500, $[\phi]_{282}$ 0, $[\phi]_{270}$ −36 700.

(1*S*,2*R*)-(+)-*trans*-*N*-5-Bromosalicylidene-2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine: $[\alpha]_D$ +392° (*c* 0.43, EtOH); ORD (*c* 0.0086, EtOH); $[\phi]_{500}$ +2190, $[\phi]_{350}$ +30 300, $[\phi]_{332}$ 0, $[\phi]_{312}$ −35 300, $[\phi]_{283}$ 0, $[\phi]_{270}$ +21 900, CD $[\theta]_{334}$ 46 000.

Pharmacology. Rabbit Hyperthermia. Male albino rabbits (2.0–2.9 kg) were employed as subjects for the hyperthermia study, since animals weighing over 3 kg show poorer responses to pyretogenic agents.[23] Prior to treatment, each rabbit was accommodated for 1 week in a restraining apparatus similar to that described by Knize et al.[9] Use of suspension restraint minimized stress-induced hyperthermia and eliminated fatalities which usually occurred during prolonged restraint in conventional rabbit boxes. A period of 1 h was generally required for the rabbit's temperature to stabilize once restrained. Colonic temperature was measured via a thermistor probe inserted 4.0 cm into the rectum and attached to a YSI Telethermometer. Temperature was monitored continuously for 4 h and recorded every 20 min postinjection. All injections were made between 1200 and 1500 h and experiments were separated by 5–7 days to minimize possible tolerance. Drugs were dissolved in pyrogen-free saline and administered aseptically into the marginal ear vein in a volume of 0.1 mL/kg. Room temperature was maintained at 24 ± 1 °C. Racemic DMCPA·HCl was given at a dose of 1.6 mg/kg and doses of the (+) and (−) isomers of DMCPA·HCl given were 0.8 mg/kg. Significant differences between treatment groups was assessed at each time using the grouped Student's *t* test.

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