Centrally Active *N*-Substituted Analogs of 3,4-Methylenedioxyphenylisopropylamine (3,4-Methylenedioxyamphetamine)

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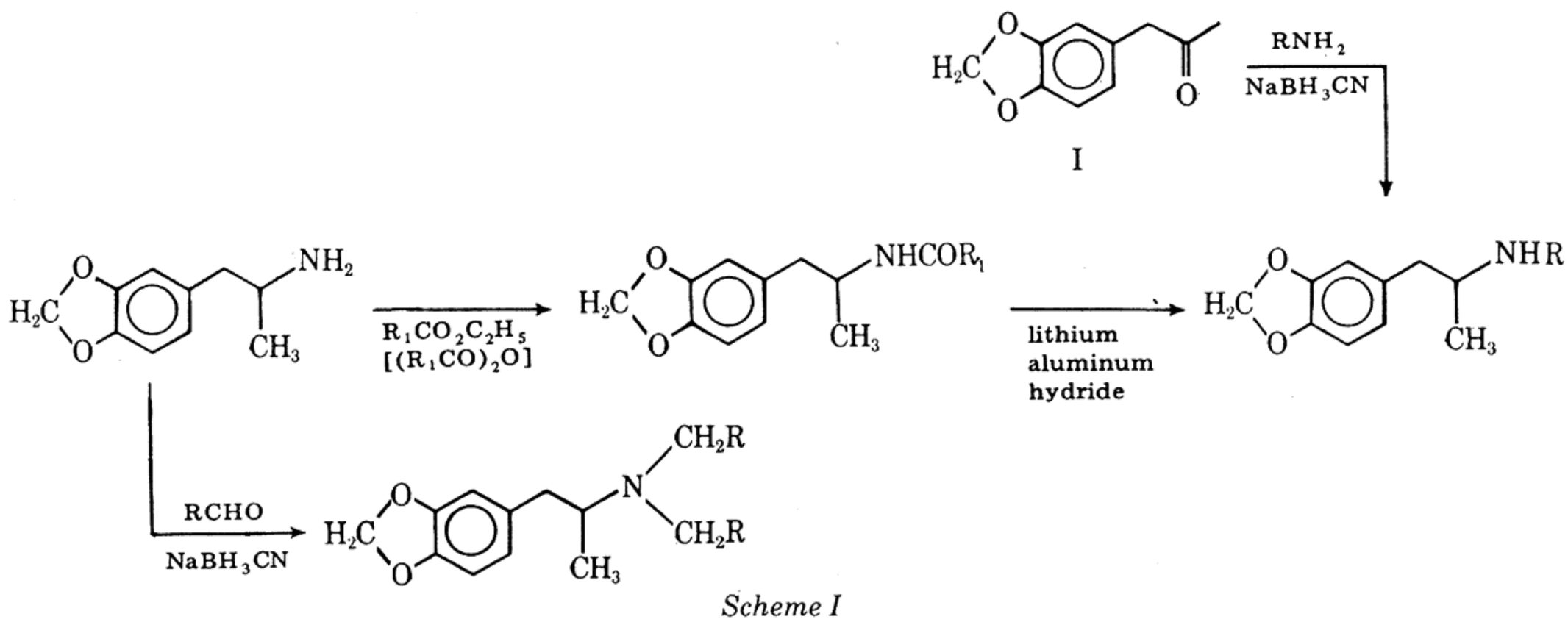
Abstract □ The known central nervous system activity of 3,4-methylenedioxyphenylisopropylamine and its *N*-methyl homolog prompted the synthesis of a series of analogs with substituents on the nitrogen atom. Most of these analogs (R = alkyl, alkenyl, hydroxy, alkoxy, and alkoxyalkyl) were prepared by the reductive alkylation of 3,4-methylenedioxyphenylacetone with the appropriate amine and sodium cyanoborohydride. Hindered isomers were synthesized indirectly. Measurements of their pharmacological activity in several animal assays and in human subjects indicated that the central activity decreased with the incr bulk of the *N*-substituent.

Keyphrases □ Amines, phenylalkyl, substituted—*N*-substitute logs of psychotomimetic agents □ Psychotomimetic agents—*N*-s tuted analogs of known centrally active agents □ 3,4-Methylene phenylisopropylamine—synthesis of centrally active *N*-substi analogs

The structural nucleus of amphetamine has served as the basis of numerous compounds of pharmacological interest. Amphetamine itself is a sympathomimetic stimulant at nominal dosages and leads to a psychotomimetic syndrome only at high dose levels (1). Nuclear alkyl stitution maintains the stimulant properties of the p compound (2, 3), but the substitution of methoxyl gr leads to compounds that are primarily psychotomir



Scheme I

(4); this property is enhanced by the additional inclusion of alkyl (5), halo (6), or alkylmercapto (7) groups. A methylenedioxy group on the aromatic nucleus, either without (8, 9) or with (10) methoxyl groups, maintains this latter pharmacological property. Removal of the α-methyl group of these substituted amphetamine analogs inevitably decreases potency but leaves their qualitative nature intact (11).

Less is known about the effects of *N*-substitution. With amphetamine itself, *N*-methylation provides methamphetamine, which is similar to amphetamine in both potency and action (12), but only sparse information exists concerning the human pharmacology of higher homologs (13). One psychotomimetic (methylenedioxyphenylisopropylamine, II*a*) is known to maintain its central action in humans with both *N*-methylation (7) and *N*-ethylation (14).

This report describes the preparation of some related *N*-substituted analogs of II*a* and outlines their pharmacological properties with respect to motor activity and analgesia in animals and central activity in humans.

RESULTS AND DISCUSSION

Several bases were prepared by one or more of the three general procedures shown in Scheme I. Procedure I, employing the reductive amination of a ketone with amines in the presence of sodium cyanoborohydride (15), gave acceptable yields with piperonylacetone (I) and most primary amines as their hydrochloride salts in methanol. The products were isolated conventionally except for the long chain homologs which, as salts, were extremely water insoluble but soluble in methylene chloride. This procedure was unsatisfactory with hindered primary amines (*tert*-butylamine and 4-aminoheptane); with the secondary amines studied, it was effective only with dimethylamine.

The simpler homologs could be prepared by acylation of II*a* itself, followed by reduction of the resulting amide with lithium aluminum hydride (Procedure II). The *N,N*-diethyl homolog II*v* could not be formed from I and diethylamine, and it was prepared by the reductive alkylation of II*a* with an excess of acetaldehyde and with sodium cyanoborohydride (Procedure III). Compound II*r* formed readily from I and hydroxylamine, but attempts to distill the isolated product led to an erratic degree of decomposition by disproportionation, in part, to II*a*. An alternative procedure leading to II*r* was the reduction of the I oxime. The product amines and their physical properties are shown in Table I. Representative synthetic procedures are outlined under *Experimental*.

Several bases were evaluated as centrally active drugs in assays that measured analgesia or motor stimulation. Analgesia studies included hot-plate and light–warmth stimuli, as well as diminished response to injected acetic acid as determined by the loss of the stretch reflex response. Motor stimulation was determined in automated activity cages. Human psychotomimetic efficacy was determined for several of these materials by standard procedures (4).

In all animal assays, II*a* was significantly more active as an analgesic than control saline. The results (Table II) were normalized with II*a* as a standard, with increasing values indicating increased effectiveness. The motor stimulation observed in mice and the effective psychotomimetic levels found in humans are given in Table III. A full report of the pharmacological procedures and related experimental details was published separately (19).

The direct determination of central activity of these materials in animal studies is compromised by the use of dosages close to the LD_{50} values and may represent a more generalized somatic challenge than simple analgesia or stimulation. This problem was apparent for higher dosages of II*a* and II*b* but not for II*m* and II*o* where there was little stimulation despite high LD_{50} levels. Throughout these assays, it was apparent that the simplest homologs of II*a* (II*b*, II*c*, and II*r*) were somewhat similar in action and efficacy. The two simplest compounds (II*a* and II*b*) have been studied most frequently, and the reported facts are compared with the results of this study in Table IV. Generally, both the toxicity (and the risk) of a drug and its central activity decrease with homologation, maintaining a constant therapeutic index. The metabolic explanation that the activity of II*b* in humans is due to its conversion to II*a* is contradicted by the qualitative differences of their actions and by the fact that opposite optical isomers are responsible for their actions (22). Compound II*r*, a potential metabolite of II*a*, has been studied only as the racemate.

EXPERIMENTAL

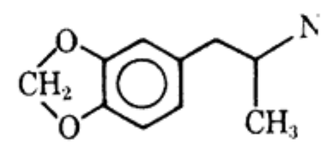
Melting points were determined in open capillaries and are uncorrected. Boiling points were recorded from bulb-to-bulb distillation. Microanalyses of all new compounds are included in Table I. All new compounds had IR and NMR spectra consistent with the assigned structures[1].

***N*-Ethyl-3,4-methylenedioxyphenylisopropylamine (II*c*)**—*Procedure I*—To a solution of 31.0 g of ethylamine hydrochloride in 110 ml of methanol were added 6.6 g of piperonylacetone (I, 37 mmoles) and then 3 g of sodium cyanoborohydride. The mixture was stirred at ambient temperature, and 12 *N* HCl was added as required to maintain the pH at neutrality (determined by the use of external damp universal pH paper). The reaction was complete in 36 hr. Following addition to 1 liter of water containing 5 ml of 12 *N* HCl, the reaction mixture was extracted twice with 150 ml of methylene chloride (discarded), made basic with 25% NaOH, and reextracted with 3 × 150 ml of methylene chloride. The extracts were pooled, and the solvent was removed *in vacuo*.

Distillation of the residual oil (8.3 g) at 0.20 mm Hg yielded 6.0 g of product as a viscous colorless oil, bp 85–95°. This product was dissolved in 60 ml of isopropanol and acidified with 12 *N* HCl (titration end-point determined with external damp universal pH paper), and an equal volume of ether was added. There was a spontaneous crystallization of the product as a white solid. It was removed by filtration and washed first

[1] IR spectra were obtained on a Perkin-Elmer Infracord spectrophotometer, and NMR spectra were obtained on a Perkin-Elmer 60-mHz permanent magnet NMR spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN 37921.

Table I—*N*-Substituted 3,4-Methylenedioxyphenylisopropylamines



Compound	R_1	R_2	Procedure	Boiling Point of Base	Melting Point of Hydrochloride	Yield, %	Analysis of Nitr % Calc.	Fou
II*a*[a]	—H	H	I[b]	80–90°/0.2 mm	187–188°	31[c]	—[d]	—
II*b*[a]	—CH_3	H	I	100–110°/0.4 mm	152–153°	74	—[e]	—
			II	100–110°/0.4 mm	151–152°	46[f]	—	—
II*c*	—CH_2CH_3	H	I	85–95°/0.2 mm	201–202°	68	5.75	5.7
			II	90–100°/0.2 mm	198–199°	37[g]	—	—
II*d*	—$(CH_2)_2CH_3$	H	I	90–100°/0.3 mm	194–195°	52	5.43	5.4
II*e*	—$CH(CH_3)_2$	H	I	95–110°/0.3 mm	186–186.5°	25	5.43	5.4
II*f*	—$(CH_2)_3CH_3$	H	I	90–100°/0.15 mm	200–200.5°	26	5.15	5.2
II*g*	—$CH_2CH(CH_3)_2$	H	I	95–105°/0.15 mm	179–180°	64	5.15	5.1
II*h*	—$CH_2CHCH_2CH_2$	H	I	90–100°/0.1 mm	218–220°	15	5.19	5.2
II*i*	—$(CH_2)_4CH_3$	H	I	110–120°/0.2 mm	164–166°	7	4.90	4.8
II*j*	—$(CH_2)_5CH_3$	H	I	135–145°/0.3 mm	188–189°	38	4.67	4.5
II*k*	—$(CH_2)_7CH_3$	H	I	130–135°/0.2 mm	206–208°	61	4.27	4.2
II*l*	—CH_2CN	H	I	150–160°/0.3 mm	156–158°	21[h]	11.00	11.0
II*m*	—CH_2CH_2OH	H	I	155–160°/0.15 mm	147–148°	35	5.39	5.4
II*n*	—$CH_2CH_2OCH_3$	H	I	100–120°/0.2 mm	182.5–183°	72	5.12	5.1
II*o*	—$CH_2CH{=}CH_2$	H	I	90–95°/0.2 mm	174–176°	39	5.48	5.3
II*p*	—$CH_2C{\equiv}CH$	H	I	105–110°/0.2 mm	189–190°	39	5.52	5.5
II*q*	—$CH_2C_6H_5$	H	I	135–145°/0.2 mm	170–171°	13	4.58	4.7
II*r*	—OH	H	I	—[i]	149–150°	31	6.05	6.0
II*s*	—OCH_3	H	I	90–95°/0.5 mm	143–146°	28	5.70	5.7
II*t*	—$NHC(CH_3)_3$	H	I	95–105°/0.1 mm	220–222° dec.	3	9.77	10.6 10.8
II*u*	—CH_3	—CH_3	I	85–90°/0.5 mm	172–173°	27	5.75	5.7
II*v*	—CH_2CH_3	—CH_2CH_3	III	85–88°/0.15 mm	177–178°	62	5.15	5.1

[a] Compound II*a* has been referred to in the literature as MDA and EA-1299. Compound II*b* has been referred to in the literature as MDM, MDMA, and EA-1475 EA codes are from the Edgewood Arsenal, U.S. Army Chemical Warfare Service. [b] Ammonia was employed as the acetate salt. [c] The conventional preparation by the lithium aluminum hydride reduction of 1-(3,4-methylenedioxyphenyl)-2-nitropropene gave a yield of 87%. [d] Lit. (16) mp 186–187°. [e] Lit. (17) mp 148–149 mp 147–148° (18). [f] Overall yield from II*a*, with isolation and purification of the intermediate formamide. [g] Overall yield from II*a*, with isolation and purification intermediate acetamide. [h] The major product was II*a* from ammonia formed by the *in situ* decomposition of cyanomethylamine. [i] Unstable to distillation (see Free base from isopropanol, mp 94–95°. Nitrogen analysis was: calc., 7.08; found, 7.09.

with isopropanol–ether and finally with ether alone, giving 6.1 g of the air-dried product (68% yield), mp 201–202°.

Procedure II—A solution of 3.6 g of II*a* as the free base (20 mmoles) in 20 ml of pyridine was treated with 2.4 ml of acetic anhydride and stirred at ambient temperature for 18 hr. The reaction mixture was added to 200 ml of water, stirred several hours, acidified with hydrochloric acid, and extracted with 2 × 80 ml of methylene chloride. The extracts were pooled, and the solvent was removed *in vacuo* to yield an off-white solid (mp 89–90°), which crystallized from 80 ml of ethyl acetate–hexane (1:1). The acetamide was obtained as white crystals (2.6 g, 58% yield, mp 92–93°).

A solution of 1.7 g of the acetamide (7.7 mmoles) in 8 ml of dry tetrahydrofuran was added to a solution of 1.6 g of lithium aluminum hydride in 150 ml of tetrahydrofuran and stirred at reflux temperature. After being held at reflux with stirring for 72 hr, the reaction mixture was cooled (external ice water), and treated sequentially with 1.6 ml of water in several milliliters of tetrahydrofuran, 1.6 ml of 15% NaOH, and fi with 4.8 ml of additional water. The white solids were removed b tration and washed with tetrahydrofuran. The filtrate and washes combined, and the solvent was removed *in vacuo*.

The residual oil was distilled (90–100° at 0.2 mm Hg), dissolved ml of isopropanol, acidified with 12 *N* HCl (external damp pH pa and diluted with ether. Resulting white solids were filtered, washed isopropanol–ether and then with ether, and air dried. The pro weighed 1.0 g, mp 198–199° (mixed melting point with the product Procedure I, 198–199°); the yield was 53% from the acetamide and overall from II*a*.

***N* - Cyanomethyl - 3,4 - methylenedioxyphenylisopropyla (II*l*)**—The crude reaction product (following Procedure I) obtained I (2.67 g, 15 mmoles), cyanomethylamine sulfate (20 g, 130 mmole 100 ml of methanol adjusted to neutral pH with 25% NaOH, and 1. sodium cyanoborohydride was a mixture of II*l* and II*a*. The latte undoubtedly formed by the *in situ* decomposition of free cyanon

Table II—Central Analgesia[a]

Compound	Hot Plate[b]	Tail Flick[c]	Stretch Reflex[d]
II*a*	1	1	1
II*b*	1.09	1.25	5.33
II*c*	1.04	0.66	0.71
II*d*	1.50	0.78	0.30
II*e*	1.00	0.90	0.22
II*f*	0.75	0.87	0.37
II*g*	1.18	0.87	0.45
II*h*	0.77	0.84	0.61
II*m*	1.99	1.08	0.26
II*n*	0.83	0.87	0.32
II*o*	1.67	1.06	0.29
II*p*	0.87	0.92	0.37
II*s*	1.34	0.86	0.36
II*u*	1.53	0.91	0.35

[a] Values obtained in mice, with oral administration, and normalized to II*a* = 1. [b] With 20 mg/kg; II*a* = 133% of saline control. [c] With 100 mg/kg; II*a* = 119% of saline control. [d] With 20 mg/kg; II*a* gave a 47% response of the saline control at 10 mg/kg, a 32% response at 20 mg/kg, and a 0% response (complete analgesia) at 100 mg/kg.

Table III—Central Stimulation

Compound	Motor Activity (Mice)[a]	Psychotomimet Activity (Humans)[b]
II*a*	640	60–120
II*b*	1530	100–160
II*c*	1780	140–200
II*d*	—	>160
II*e*	910	>160
II*n*	176	>160
II*o*	153	>160
II*p*	—	>160
II*q*	—	>160
II*r*	—	80–120
II*s*	149	>160
II*u*	40	>160
Saline	160	

[a] Averaged activity responses (events per hour) 1–4 hr following drug ad tration (20 mg/kg po). [b] Range of effective dosages, in milligrams, orally. given as greater than (>) represent the absence of significant activity at this imum dosage.

Table IV—Comparison of Pharmacological Properties of II*a* and II*b*

Assay	Species	II*a*	II*b*	Reference[a]
Toxicity, LD_{50}, mg/kg	Mouse (intraperitoneal)	68	97	20
	Rat (intraperitoneal)	27	49	20
	Guinea pig (intraperitoneal)	60	98	20
	Dog (intravenous)	7	14	20
	Monkey (intravenous)	6	22	20
Central analgesia	Mouse, relative potency at stated dosages			
	hot plate (20 mg/kg)	1	1.09	—
	tail flick (100 mg/kg)	1	1.38	—
	stretch reflex (20 mg/kg)	1	5.34	—
Central stimulation	Mouse, relative potency at 20 mg/kg	1	2.4	—
	Dog, mg/kg	0.5–15	5–50	20
	Monkey, mg/kg	1–20	10–75	20
Human activity	Man			
	active dosage, mg	60–120	100–160	8, 9, 21
	active isomer	*R*[b]	*S*[b]	22
	qualitative feature	Moderately complex	Simple	7, 9, 23

[a] Published literature data have been commingled with results from this study for comparison. [b] *R* and *S* represents the absolute configurations of the pharmacologically active isomers, and are the levo- and dextrorotatory forms, respectively.

ylamine to ammonia. Upon distillation, the first fraction (1.3 g, bp 90–110° at 0.4 mm Hg) was substantially free of the cyanomethylene group (by NMR), but the second fraction (0.8 g, bp 150–160° at 0.3 mm Hg) had the proper NMR spectrum in deuterium oxide as the hydrochloride salt: δ 1.30 and 1.42 (2s, 3H, CH_3), 3.00 (m, 2H, aromatic CH_2), ~3.6 (m, 1H, CH), 4.38 (s, 2H, CH_2CN), 4.75 (s, NH and DOH), 6.05 (s, 2H, OCH_2O), and 6.95 (s, 3H, aromatic H). The analytical sample was recrystallized from boiling isopropanol (50 ml/g).

***N*-Hydroxy-3,4-methylenedioxyphenylisopropylamine (II*r*)**—The crude reaction product (*via* Procedure I) obtained from I (7.2 g, 40 mmoles), hydroxylamine hydrochloride in methanol (29.6 g in 240 ml), and sodium cyanoborohydride (2 g) gave evidence, on attempted distillation, of the generation of water by pyrolytic disproportionation. At bath temperatures of <90°, the distillate was mainly II*t*; but above 100°, there was extensive decomposition to II*a*, which was the major product isolated (verified by IR spectral comparison of the hydrochloride salt with reference II*a*·HCl). The free base could be obtained as a solid and was best purified by recrystallization as described below.

Compound II*r* also could be prepared *via* the I oxime. A solution of 10 g of I (56 mmoles) and 10 g of hydroxylamine hydrochloride in 50 ml of pyridine and 50 ml of ethanol was held at reflux for 2 hr. Removal of the solvents *in vacuo* left an oil, which crystallized upon trituration under water. The crude oxime was removed by filtration and recrystallized from ethanol–water to yield 5.5 g (51% yield) of a white crystalline product, mp 84–87°. The oxime was dissolved in 50 ml of methanol and treated with 2.5 g of sodium cyanoborohydride. While being stirred at ambient temperature, 12 *N* HCl was added dropwise (about 10 drops every 12 hr) over 3 days. The methanol was removed *in vacuo*, and the residue was suspended in acidified water (5 ml of 12 *N* HCl in 500 ml). The reaction mixture was extracted with 3 × 100 ml of methylene chloride (unreacted oxime was discarded), made basic with sodium hydroxide, and reextracted with 3 × 100 ml of methylene chloride. The extracts were pooled, and the solvent was removed *in vacuo* to provide II*r* (free base) as a white solid (1.4-g crude yield after vacuum drying at 0.2 mm Hg).

After recrystallization from isopropanol (6 ml/g), the product had a melting point of 92–94° (mixed melting point with the oxime, 56–62°). In the IR spectrum, both the NH and the OH stretch vibration absorptions were visible at 3040 (broad) and 3135 (sharp) cm^{-1} (in mineral oil). The free base was converted to the hydrochloride salt by dissolution in 20 ml of warm isopropanol, acidification with 12 *N* HCl (external damp pH paper), and the addition of 200 ml of ether. The clear solution slowly deposited white crystals of II*r*·HCl, 0.8 g (12% yield from the oxime, overall yield of 6%), mp 149–150° (mixed melting point with II*a*·HCl was 128–138°).

***N,N*-Diethyl-3,4-methylenedioxyphenylisopropylamine (II*v*) (Procedure III)**—A stirred solution of 1.4 g of II*a*·HCl (6.5 mmoles) in 30 ml of methanol was treated with 7.0 g of acetaldehyde and 1.5 g of sodium cyanoborohydride. Then 12 *N* HCl was added dropwise as needed to maintain the pH at neutrality (as determined by external damp universal pH paper). After 48 hr, the reaction mixture was added to 600 ml of water, acidified with hydrochloric acid (5 ml), and extracted with 2 × 100 ml of methylene chloride. The residual aqueous phase was made basic with 25% NaOH and reextracted with 3 × 100 ml of methylene chloride. The extracts were combined and the solvent was removed *in vacuo*. The residual pale-yellow oil (1.1 g of crude weight) was distilled (85–88° at 0.15 mm Hg) to yield 1.0 g of a colorless oil. This oil was dissolved in 8 ml of isopropanol, acidified with 12 *N* HCl, and diluted with 30 ml of ether. After the product had crystallized completely, it was removed by filtration and washed first with 75% ether (with isopropanol) and finally with ether. Air drying yielded 1.1 g of II*v*·HCl as white crystals (62% of theory), mp 177–178°.

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