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ACKNOWLEDGMENTS

Presented in part at the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, Chicago meeting, August 1974.

Supported by National Cancer Institute Grant CA-17625 and American Cancer Society Grant CH-19 to K. H. Lee.

The authors thank Dr. Tohru Kikuchi, Research Institute for Wakan-Yaku (Oriental Medicines), University of Toyama, Toyama, Japan, for providing authentic samples of β-amyrin acetate, lupeol acetate, epifriedelanol, and stigmasterol; Dr. D. L. Harris, Department of Chemistry, University of North Carolina at Chapel Hill, for the 100-MHz NMR spectra; and Dr. David Rosenthal and Mr. Fred Williams, Research Triangle Center for Mass Spectrometry, for mass spectral data.

Convenient Synthesis of (*S*)-(+)-Apomorphine from (*R*)-(−)-Apomorphine

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Abstract □ A method was devised for preparing (*S*)-(+)-apomorphine from (*R*)-(−)-apomorphine. Dehydrogenation of the dimethyl ether of (*R*)-(−)-apomorphine with 10% palladium-on-carbon followed by reduction with sodium cyanoborohydride under acidic conditions resulted in quantitative racemization to give (*R,S*)-apomorphine dimethyl ether, which then was resolved with (−)-tartaric acid. Ether cleavage of (*S*)-(+)-apomorphine dimethyl ether (−)-tartrate with hydriodic acid in acetic anhydride yielded (*S*)-(+)-apomorphine, which was isolated as the hydrochloride salt in 99% enantiomeric excess.

Keyphrases □ Apomorphine—synthesis of (*S*)-(+)-stereoisomer from (*R*)-(−)-stereoisomer □ Dopaminergic agonists—apomorphine, synthesis of (*S*)-(+)-stereoisomer from (*R*)-(−)-stereoisomer □ Stereoisomers—apomorphine, synthesis of (*S*)-(+)-stereoisomer from (*R*)-(−)-stereoisomer

Current interest in apomorphine (I) stems from its activity as a dopaminergic agonist and its consequential antiparkinsonism activity (1–3). Clinical utility has been demonstrated for I alone and in combination with other agents such as levodopa (4). Further studies are aimed at preparing suitable prodrug derivatives to overcome the drawbacks to its use (5). In addition to parkinsonism, recent studies indicated potential new uses for I in ameliorating the symptoms of Huntington's chorea (6), tardive dyskinesia (7), Gilles de la Tourette's syndrome (8), and schizophrenia (9, 10).

BACKGROUND

Most work to date involved the use of (−)-apomorphine (*R*-configuration), synthesized commercially by the acid-catalyzed rearrangement of (−)-morphine (11). Investigations into the pharmacological properties of (*S*)-(+)-apomorphine (II) have been limited to *in vivo* assays including dog emesis, a caudate brain-lesioned mouse preparation (12, 13), and evaluation of the racemate in comparison to (*R*)-(−)-I in these assays as well as on overt behavior in the monkey (13, 14). Previous reports utilized a *de novo* synthesis of (*R,S*)-I *via* Pschorr cyclization followed by resolution of the racemate (12, 15).

Molecular pharmacologists have extended the knowledge of dopaminergic mechanisms by the examination of several receptor assays, culminating in the postulation of several distinct dopamine receptors (16). Along with other criteria, these receptors are distinguished from one another by the differential action of dopaminergic agonists and antagonists, including (*R*)-(−)-I. Thus, apparently difficult to rationalize effects, such as the improvement of schizophrenic symptoms with exceedingly low doses of I, possibly can be understood on the basis of presynaptic dopamine receptors modulating dopaminergic transmission and, consequently, postsynaptic dopaminergic activity (9).

Because of the renewed interest in apomorphine pharmacology and the known differential receptor activity of stereoisomeric pharmacological agents (17), a reexamination of the two antipodes of I was desired. Also, a more direct method was sought for the synthesis of II from the commercially available (*R*)-(−)-antipode rather than the *de novo* synthesis. The synthesis of II reported here is patterned after an earlier procedure for racemization of the related aporphine alkaloid glaucine (18).

EXPERIMENTAL

Reagents—(*R*)-(−)-Apomorphine hydrochloride hemihydrate[1], 10% palladium-on-carbon[2], sodium cyanoborohydride[3], (+)- and (−)-tartaric acid[3], *p*-tolylsulfonylmethylnitrosamide[3], and heptafluorobutyric an-

[1] McFarland Smith Ltd., Edinburg, Scotland.
[2] Alfa-Ventron, Danvers, Mass.
[3] Aldrich Chemical Co., Milwaukee, Wis.

0022-3549/80/0900-1056$01.00/0

hydride[4] were used without further purification. All other solvents and reagents were analytical reagent grade or better.

Spectral Studies—PMR spectra were obtained on a 60-MHz[5] or a 100-MHz[6] spectrometer, and chemical shifts are reported relative to tetramethylsilane. Optical rotations were analyzed on a spectropolarimeter[7]. Melting points were taken on a digital melting-point analyzer[8] and are corrected. Mass spectra were obtained on a medium-resolution mass spectrometer[9] by direct-probe insertion.

TLC was performed on 0.25-mm silica gel plates[10] that were developed with benzene–methanol (4:1). Plates were visualized under short (254 nm) and long (280 nm) wavelength UV light. GLC of apomorphine was conducted as its *O,O*-heptafluorobutyryl derivative as described previously (19). Apomorphine dimethyl ether also was analyzed using this GLC procedure.

Synthesis of (*R*)-(−)-Apomorphine Dimethyl Ether (III)—(*R*)-(−)-Apomorphine hydrochloride was converted to III by the method of Neumeyer *et al.* (13) using ethereal diazomethane. The free base was crystallized from *n*-hexane[11] to yield pale-yellow needles, mp 75–77° [lit. (20) mp 77.5–79°], $[\alpha]_D^{22}$ −142° (*c*, 1.59 in absolute ethanol) [lit. (21) $[\alpha]_D^{22}$ −148° (*c*, 1.64 in absolute ethanol)]; PMR (100 MHz, $CDCl_3$): δ 2.54 (s, 3H, *N*-CH_3), 2.15–3.30 (m, 7H, aliphatic), 3.71 (s, 3H, C_{11}-OCH_3), 3.88 (s, 3H, C_{10}-OCH_3), 6.84 (m, 2H, H-8 and H-9), 7.07 (m, 1H, H-2), 7.25 (m, 1H, H-3), and 8.25 (dd, 1H, H-1), identical in all respects to the reported spectrum (15); mass spectrum: *m/e* (%) 295 (68) (M^+), 294 (100), 281 (20), 264 (18), and 252 (18).

Synthesis of 6a,7-Dehydroapomorphine Dimethyl Ether (IV)—Compound III (2 g, 6.8 mmoles) was refluxed with 2 g of 10% palladium-on-carbon in 100 ml of acetonitrile under a dry nitrogen atmosphere according to the method of Cava *et al.* (22). TLC analysis indicated complete conversion in 8 hr (R_f of III = 0.50, R_f of IV = 0.85). The catalyst was removed by filtration through sintered glass and was washed repeatedly with acetonitrile. The filtrate was taken to dryness *in vacuo* to give a dark-green oil (1.9 g). This product gave a single spot on TLC and was used without further purification; PMR (60 MHz, $CDCl_3$): δ 3.09 (s, 3H, *N*-CH_3), 3.35 (s, 4H, CH_2CH_2), 3.94 (s, 3H, C_{11}-OCH_3), 4.00 (s, 3H, C_{10}-OCH_3), 6.68 (s, 1H, H-7), 7.0–7.6 (m, 4H, aromatic), and 9.65 (dd, 1H, H-1); mass spectrum: *m/e* (%) 293 (100) (M^+), 278 (80), 263 (12), 250 (25), and 235 (50).

Synthesis of (*S*)-(+)-Apomorphine Dimethyl Ether (V)—Compound IV (1.9 g, 6.5 mmoles) was dissolved in 250 ml of absolute ethanol with heat. The solution and the reaction mixture to follow were purged continuously with dry nitrogen and constant stirring. Sodium cyanoborohydride (2.0 g, 32 mmoles) was added, and the reaction was initiated and maintained at an apparent pH of 5.0 by periodic additions of ethanolic hydrochloric acid. After 18 hr, an additional 2 g of sodium cyanoborohydride was added and the reaction was allowed to continue for 2 hr, at which time TLC analysis indicated a complete conversion to (*R,S*)-apomorphine dimethyl ether. The reaction mixture was taken to dryness *in vacuo*, and the residue was solubilized in 150 ml of water, alkalinized with potassium carbonate, and extracted with ethyl acetate (3 × 200 ml). The organic layer was washed with 50 ml of water, dried with anhydrous sodium sulfate, and taken to dryness *in vacuo* to give a gold oil (1.85 g), $[\alpha]_D^{22}$ −9.2° (*c*, 1.5 in absolute ethanol, indicating 97% racemization). The PMR and mass spectra were identical to those given for III.

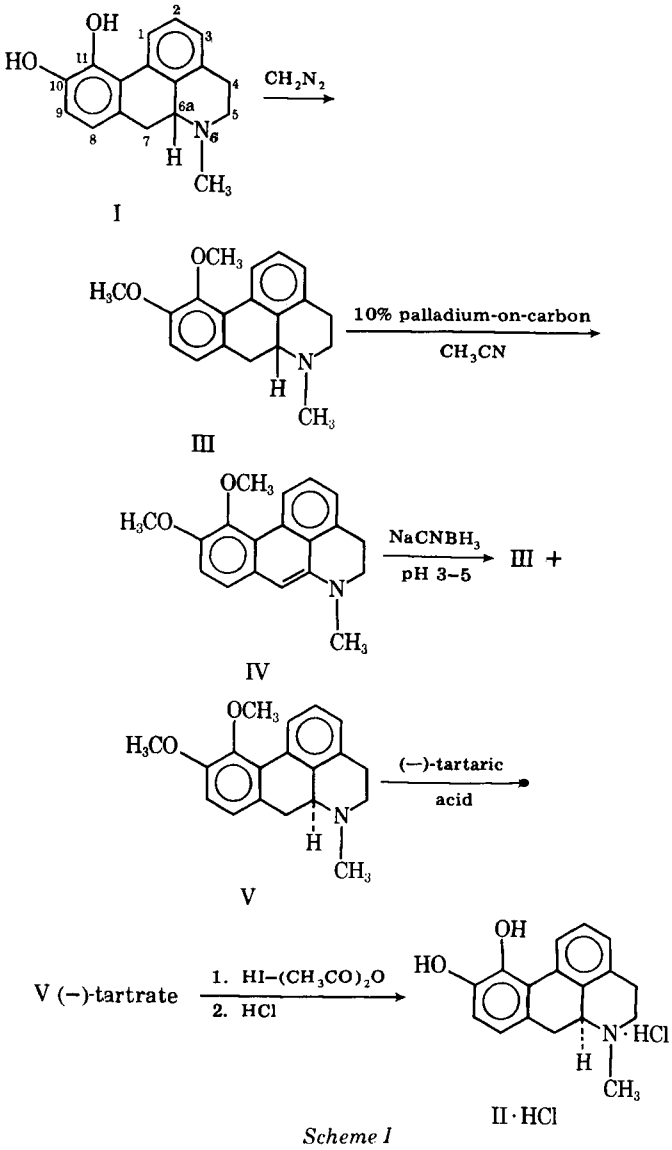
The racemate (1.85 g) was dissolved in 10 ml of absolute ethanol and filtered. A filtered solution of 1.2 g (−)-tartaric acid (8.0 mmoles) in 17 ml of absolute ethanol was added, and the cloudy solution was heated to clarification. The white granular crystals that separated (1.15 g) were washed with ethyl acetate and recrystallized repeatedly from absolute ethanol to yield 0.635 g of (*S*)-(+)-apomorphine dimethyl ether (−)-tartrate, $[\alpha]_D^{22}$ +62.1° (*c*, 2.06 in water) [lit. (12) $[\alpha]_D^{22}$ +64.0° (*c*, 1 in water)], mp 189–191° dec. [lit. (12) mp 179–184° dec.]. Authentic (*R*)-(−)-apomorphine dimethyl ether (+)-tartrate prepared from pure (*R*)-(−)-IV (prepared as described) gave $[\alpha]_D^{22}$ −60.0° (*c*, 1 in water) [lit. (12) $[\alpha]_D^{22}$ −59.6° (*c*, 1 in water)], mp 186–187° [lit. (12) mp 177–183°].

***S*-(+)-Apomorphine (II) Hydrochloride**—The free base V was generated from 300 mg of the (−)-tartrate salt prepared by extraction from 10 ml of saturated sodium bicarbonate solution with ethyl acetate (3 × 25 ml). The organic layer was washed once with 10 ml of water, dried *in vacuo*, and dried further by azeotroping twice with 10 ml of benzene. The ether functions were cleaved using hydriodic acid–acetic anhydride according to the method of Neumeyer *et al.* (15) as modified by Saari *et al.* (12). The reaction was monitored by TLC and was complete in 30 min. The reaction was adjusted carefully to pH 7–8 with saturated sodium bicarbonate containing 20 mg of dithionite as an antioxidant and exhaustively extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and taken to dryness *in vacuo*.

The product was dissolved in ether and filtered, and hydrogen chloride was passed through to yield the hydrochloride salt as a white powder. This powder was collected by filtration and dried *in vacuo* at 65° for 18 hr to give 104 mg (50%) of II·HCl, $[\alpha]_D^{22}$ 47.4° (*c*, 1.13 in 0.02 *N* HCl) [(*R*)-(−)-apomorphine hydrochloride gave $[\alpha]_D^{22}$ −48.7°; lit. (23) $[\alpha]_D^{22}$ −49–−51°], indicating 99% enantiomeric excess. UV comparison to (*R*)-(−)-apomorphine indicated 98.8% purity (λ_{max} 275 nm, ε 17,300), mp 249–260° dec. [lit. (12) mp 258–268° dec.]; mass spectrum: *m/e* (%) 267 (78) (M^+), 266 (100), 250 (22), 224 (34), and 221 (23), identical to the spectrum of (*R*)-(−)-apomorphine hydrochloride. GLC analysis indicated cochromatography with authentic (*R*)-(−)-apomorphine [as the heptafluorobutyryl derivative (19)] and >99% purity.

RESULTS AND DISCUSSION

Interest in racemizing and resolving aporphines continues because naturally occurring aporphines and aporphines generated from natural products [*e.g.*, (−)-apomorphine from (−)-morphine (11)] usually exist as single antipodes. A recent study (24) allowed for the racemization and resolution of the catatonic aporphine (+)-bulbocapnine by a route similar to that described in this study (Scheme I).



Scheme I

[4] Pierce Chemical Co., Rockford, Ill.
[5] Model R12-A, Perkin-Elmer Corp., Norwalk, Conn.
[6] Model HA-100, Varian Associates, Palo Alto, Calif.
[7] Model 241MC, Perkin-Elmer Corp., Norwalk, Conn.
[8] Model 355, Fisher Scientific Co., Houston, Tex.
[9] Model 21491, Dupont Instrument Products Division, Wilmington, Del.
[10] Polygram silica G/V_{254}, Brinkmann Associates, Westbury, N.Y.
[11] Skelly B.

This reported preparation of (*S*)-(+)-apomorphine represents a facile conversion of the readily available (*R*)-(−)-antipode rather than a *de novo* synthesis of the aporphine skeleton by Pschorr cyclization (12, 15). Due to the instability of the catechol, a protecting group was necessary for subsequent reactions; the dimethyl ether was chosen because of its ease of preparation and subsequent removal (12, 15).

The racemization of III was accomplished in the manner used previously for the preparation of racemic glaucine, which involved oxidation to the dehydroaporphine followed by nonstereospecific reduction (18). While the first step was accomplished earlier by oxidation with iodine and sodium acetate (25) or with mild permanganate oxidation (26), the method described recently (22) of refluxing the aporphine in acetonitrile with 10% palladium-on-carbon proved to be a clean and facile route to IV. The dehydroaporphine corresponding to III exhibited a characteristic PMR spectrum consisting of a relatively deshielded *N*-methyl substituent (δ 3.09 *versus* 2.54 in III) as well as the signal for the H-1 proton (δ 9.65 *versus* 8.25 in III) (26). In addition, the four H-4 and H-5 protons of IV resonated as a broad singlet (δ 3.35) and the H-7 proton resonated as a singlet at δ 6.68. The same characteristics were observed in 6a,7-dehydroglaucine (18) and *O,O*-diacetyl-6a,7-dehydroapomorphine (27).

The dehydroaporphine IV is reduced easily using sodium cyanoborohydride at acidic pH, probably due to an increased development of 6,6a-quaternary imine character under acidic conditions. Other reduction methods such as dissolving metal (28) and catalytic reduction with Adam's catalyst in acetic acid have been used. Some investigators reported a sluggish reaction in the latter case (28). The sodium cyanoborohydride procedure provided a facile and nearly quantitative racemization of IV with inexpensive reagents. The method of Kametani *et al.* (29) also has been used for similar reactions, but this method requires longer reaction times, an apparatus for hydrogenation at atmospheric pressure, and, in most cases, a weight of the expensive Adam's catalyst equal to the weight of the alkaloid.

Resolution of the racemate of apomorphine dimethyl ether was accomplished in a manner similar to that of Saari *et al.* (12). In the present study, however, oiling was encountered repeatedly using ethanol–ethyl acetate as recommended by these investigators (12). Recrystallization from ethanol ultimately was more satisfactory. Repeated recrystallization gave V as the (−)-tartrate salt in 99% enantiomeric excess. The protecting groups were removed by hydriodic acid in acetic anhydride (12, 15). In alternative experiments, TLC and GLC evidence indicated smooth cleavage using boron tribromide in methylene dichloride using a literature method (30) (*i.e.*, when the solvent was not freed of ethanol prior to use).

The (*S*)-(+)-apomorphine hydrochloride isolated through the reactions indicated in Scheme I was in >99% enantiomeric excess and was >98% pure by UV spectroscopy when compared to authentic I. Considerable variability of the optical rotation was observed with high dilutions of the salt (from −74° at *c* 0.16 to −49° at *c* 1.03 or above in 0.02 *N* HCl). Thus, a minimum *c* value of 1.0 was necessary for obtaining accurate optical rotation data. This phenomenon may be attributable to the salt–free base equilibrium, which favors the latter at high dilution. Indeed, when samples were run in 0.2 *N* HCl, lower values were obtained (−63–−47° for the concentration range).

The (*S*)-(+)-compound prepared was submitted for preliminary *in vitro* pharmacological evaluation. In the presynaptic dopaminergic receptor assay of Steinsland and Heible (31), the agent exhibits 1% of the activity of (*R*)-(−)-I, as expected based on its optical purity and its expected inactivity as a dopaminergic agonist (12). However, preliminary results in the receptor assay of Seeman *et al.* (32) show an unexpected affinity similar to that of I. Complete pharmacological evaluation of II will be the subject of a subsequent report from these laboratories.

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ACKNOWLEDGMENTS

Supported by Grant NS-12259 from the National Institute of Neurological and Communicative Disorders and Stroke.