(6) K. W. Bentley and H. M. E. Cardwell, *J. Chem. Soc.*, 3252 (1955); H. Mackay and D. Crowfoot Hodgkin, *ibid.*, 3261 (1955); H. Rapoport and G. B. Payne, *J. Org. Chem.*, **15**, 1093 (1950); H. Rapoport and G. B. Payne, *J. Amer. Chem. Soc.*, **74**, 2630 (1952); H. Rapoport and J. B. Lavigne, *ibid.*, **75**, 5329 (1953).
(7) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953); A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

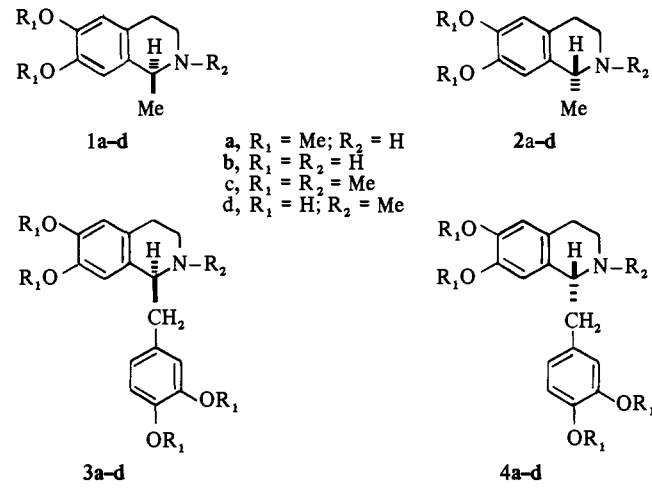
Alkaloids in Mammalian Tissues. 2.[1] Synthesis of (+)- and (−)-1-Substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines

S. Teitel,* J. O'Brien, and A. Brossi

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received January 27, 1972*

It has been suggested that dopamine and acetaldehyde or 3,4-dihydroxyphenylacetaldehyde condense in mammalian tissues to afford 1-substituted tetrahydroisoquinoline "alkaloids" which could induce a variety of pharmacological responses.[2-8] However, such *in vivo* reactions might be catalyzed by enzymes to form a single optical isomer which can expected to differ from its antipode in biological activity.[9,10] Thus, to evaluate this concept of "alkaloid" formation in man, especially in relation to the behavioral changes induced by alcoholism and to other disorders, both optical isomers are necessary.

Based on this consideration, the enantiomeric salsolinols **1b** and **2b** and tetrahydropapaverolines **3b** and **4b** were synthesized by O-demethylation of the corresponding known isomeric salsolidines[11,12] **1b** and **2b** and norlaudanosines[13] **3b** and **4b** and further characterized as their *N*-methyl derivatives. The assignment of their absolute configuration was substantiated by conversion of **1b** and **3b** into (*S*)-carnegine (1c) and (*S*)-laudanosine (3c), respectively.



Experimental Section†

(−)-(1*S*)-6,7-Dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide [(*S*)-(−)-Salsolinol Hydrobromide] (1b·HBr). A solution of 20 g (0.1 mole) of (*S*)-(−)-salsolidine[12] (**1a**), mp 47–48° [α]D −59.1° (*c* 4, EtOH) [lit.[11] mp 47.5–48.5°, [α]^{16}D −59.7° (*c* 20, EtOH)], in 200 ml of 48% HBr was refluxed for 10 hr, cooled, and evaporated under reduced pressure. The residue was crystallized from a mixture of EtOH–Et_2O to give 17.7 g (68%) of **1b·HBr**: mp 174–175°; [α]D −30.9° (MeOH); nmr δ 1.51 (d, 3, *J* = 7 Hz, CH_3), 2.70–3.40 (m, 4, CH_2CH_2), 4.35 (b, 1, CH), 6.54, 6.60 (2s, 2, aromatics), 8.50–9.50 (b, 4, 2 OH and N^+H_2); uv_{max} 225 nm (ε 6450) (infl), 288 (3890); ORD (*c* 0.27, MeOH) $[\phi]_{700}$ −63°, $[\phi]_{589}$ −65°, $[\phi]_{298}$ 0° (pk), $[\phi]_{270}$ −1570° (tr), $[\phi]_{262}$ −1450° (pk), $[\phi]_{242}$ −3370° (tr), and $[\phi]_{228}$ −1930° (pk); CD (*c* 0.001 *M*, MeOH) $[\theta]_{310}$ 0, $[\theta]_{285}$ +1160, $[\theta]_{241}$ −960, and $[\theta]_{215}$ +3770. *Anal.* ($C_{10}H_{13}NO_2$·HBr) C, H, N.

(+)-(1*R*)-6,7-Dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide [(*R*)-(+)-Salsolinol Hydrobromide] (2b·HBr). In a manner similar to the procedure for **1b**·HBr, 10 g (0.05 mole) of (*R*)-(+)-salsolidine[12] (**2a**), mp 47–48°, [α]D +59.0° (*c* 2, EtOH) [lit.[11] mp 47.5–48.5°, [α]^{16}D +59.9° (*c* 25, EtOH)], was O-demethylated to give 9 g (69%) of **2b**·HBr: mp 174–175°; [α]D +30.0° (MeOH); identical in nmr and uv with **1b**·HBr; ORD and CD mirror images of **1b**·HBr. *Anal.* ($C_{10}H_{13}NO_2$·HBr) C, H, N.

(1*S*)-6,7-Dihydroxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide [(*S*)-*N*-Methylsalsolinol Hydrobromide] (1d·HBr). To a solution of 7.3 g (0.033 mole) of (*S*)-(−)-carnegine[12] (1c), oil, [α]D −24.3° (*c* 2, EtOH) [lit.[11] oil, [α]^{18}D −24.4° (*c* 9, EtOH)], in 50 ml of CH_2Cl_2 at −70° was added over 15 min 30 ml of 5% BBr_3 in CH_2Cl_2. After stirring at 25° for 17 hr, the reaction mixture was cooled to 4°, and 100 ml of MeOH was added over 15 min and then evaporated. The residue was crystallized from a mixture of EtOH–Et_2O to give 8 g (89%) of **1d·HBr**: mp 180–182°; [α]D 0°; $[\alpha]_{365}$ +37°; nmr δ 1.55 (d, 3, *J* = 6.5 Hz, CH_3CH), 2.82 (s, 3, CH_3N), 2.70–3.70 (m, 4, CH_2CH_2), 4.43 (q, 1, *J* = 6.5 Hz, CH), 6.58 (s, 2, aromatic), 8.88, 9.02 (2s, 2, 2 OH), 10.10 (b, 1, N^+H); uv_{max} 225 nm (ε 6750) (infl), 288 (4000); ORD (*c* 0.274, MeOH) $[\phi]_{700}$ −7°, $[\phi]_{589}$ −3°, $[\phi]_{299}$ +2250° (pk), $[\phi]_{279}$ −1250° (tr), $[\phi]_{238}$ +1000° (pk), and $[\phi]_{225}$ −3500° (tr); CD (*c* 0.01 *M*, MeOH) $[\theta]_{306}$ 0, $[\theta]_{280}$ +2500, $[\theta]_{250}$ 0, $[\theta]_{234}$ 4100, $[\theta]_{220}$ +2000, and $[\theta]_{210}$ +11000. *Anal.* ($C_{11}H_{15}NO_2$·HBr) C, H, N.

(1*R*)-6,7-Dihydroxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide [(*R*)-*N*-Methylsalsolinol Hydrobromide] (2d·HBr). By the procedure given for the preparation of **1d**·HBr, 5.8 g (0.026 mole) of (*R*)-(+)-carnegine[12] (**2c**), oil, [α]D +24.6° (*c* 2, EtOH) [lit.[11] oil, [α]^{19}D +24.6° (*c* 3, EtOH)], afforded 7.1 g (85%) of **2d**·HBr: mp 180–182°; [α]D 0°; $[\alpha]_{365}$ −36.1°; identical in nmr and uv with **1d**·HBr; ORD and CD mirror images of **1d**·HBr. *Anal.* ($C_{11}H_{15}NO_2$·HBr).

Conversion of (*S*)-(−)-Salsolinol Hydrobromide (1b·HBr) into (*S*)-(−)-Carnegine (1c). To a solution of 1.5 g (5.8 mmoles) of **1b**·HBr in 50 ml of MeOH was added an excess of CH_2N_2 in Et_2O. The mixture was stored at 4° for 4 hr and then at 25° overnight. The resulting solution was evaporated at 40° in a stream of N_2, and the residue suspended in dilute $NaHCO_3$ and extracted with EtOAc. The extract was evaporated to leave 1 g (82%) of **1c** as an oil, identical in [α]D and nmr with authentic **1c**.[11]

(−)-(1*S*)-1-(3,4-Dihydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*S*)-(−)-Tetrahydropapaveroline Hydrochloride] (3b·HCl). Resolution of (±)-*N*-norlaudanosine[14] (tetrahydropapaverine) with (−)-diacetone-2-keto-L-gulonic acid[15] in *i*-PrOH afforded 67% of (*S*)-(−)-*N*-norlaudanosine (**3a**): mp 98–99°; [α]D −28.1° ($CHCl_3$) [lit. mp 97.5–98.5°,[13] [α]D −21° ($CHCl_3$)[16]].

A solution of 3 g (8.8 mmoles) of **3a** in 30 ml of 55% HI was stirred at 125° for 30 min and evaporated under reduced pressure. The residue was dissolved in 30 ml of H_2O, cooled to 4°, and adjusted under a N_2 atmosphere to pH 8 with NH_4OH. The precipitate was collected under N_2, dissolved in 30 ml of hot 6 *N* HCl, and stored at 4° overnight. The crystals were filtered and dried to give 2 g (70%) of **3b**·HCl: mp 285–286°; [α]D −32.0°. An analytical specimen prepared from 6 *N* HCl exhibited: mp 285–286°; [α]D −32.4°; nmr δ 2.70–3.40 (m, 6, 3 CH_2), 4.37 (m, 1, CH), 6.65–6.80 (m, 5, aromatic), 7.40 (b, 2, 2 OH), 9.15 (b, 2, N^+H_2); uv_{max} 230 nm (ε 11,100) (infl), 286 (6700); ORD (*c* 0.324, MeOH) $[\phi]_{600}$ −92°, $[\phi]_{589}$ −95°, $[\phi]_{301}$ +2650° (pk), $[\phi]_{285}$ −6000° (tr), $[\phi]_{256}$ −2750° (pk), $[\phi]_{233}$ −5000° (tr), and $[\alpha]_{220}$ −2500°; CD (*c* 0.01 *M*, MeOH) $[\theta]_{320}$ 0, $[\theta]_{293}$ +6300, $[\theta]_{280}$ 0, $[\theta]_{276}$ −500, $[\theta]_{264}$ 0, $[\theta]_{235}$ +600, and $[\theta]_{220}$ 0. *Anal.* ($C_{16}H_{17}NO_4$·HCl) C, H, N.

†All melting points (corrected) were taken in open capillary tubes with a Thomas-Hoover melting apparatus. The ultraviolet spectra were measured in EtOH with a Cary recording spectrophotometer Model 14M. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 spectrophotometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. Optical rotations were measured with a Perkin-Elmer polarimeter Model 141 at 25° using a 1% solution in H_2O unless noted otherwise. Rotatory dispersion curves were determined at 23° with a Durrum-Jasco spectrophotometer Model 5 using 1-cm, 0.1-cm, or 0.1-mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. Analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.35% of the theoretical values. Water of crystallization in compounds **3d**·HBr and **4d**·HBr was determined with the Karl Fischer reagent.

(+)-(1*R*)-1-(3,4-Dihydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*R*)-(+)-Tetrahydropapaveroline Hydrochloride] (4b·HCl). The above mother liquors, obtained from the treatment of tetrahydropapaverine with (−)-diacetone-2-keto-L-gulonic acid, were neutralized and resolved with (−)-di-*O*-*p*-toluoyl-*d*-tartaric acid in MeOH to afford 33% of (*R*)-(+)-*N*-norlaudanosine (4a): mp 98–99°; [α]D +28.4° ($CHCl_3$) [lit.[13] mp 97.5–98.5°, [α]D +26° ($CHCl_3$)].

In a manner similar to the procedure given for 3b·HCl, 4a was O-demethylated to give 77% of 4b·HCl: mp 285–286°; [α]D +32.1°; identical in nmr and uv with 3b·HCl; ORD and CD mirror images of 3b·HCl. *Anal.* ($C_{16}H_{17}NO_4$·HCl) C, H, N.

(+)-(1*S*)-1-(3,4-Dihydroxybenzyl)-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide Hemihydrate [(*S*)-(+)-Laudanosoline Hydrobromide] (3d·HBr). Reductive alkylation of 3a with CH_2O in the presence of Raney nickel afforded 78% of (*S*)-(+)-laudanosine (3c): mp 84–85°; [α]D +99.1° (EtOH) [lit.[17] mp 89°, [α]D +100° (EtOH)].

A solution of 6 g (16.8 mmoles) of 3c in 60 ml of 48% HBr was refluxed for 3 hr and stored at 4° overnight. The crystals were filtered and dried to give 4.8 g (74%) of 3d·HBr: mp 124–125°; [α]D +57.3°. An analytical specimen prepared from 24% HBr exhibited: mp 124–125°; [α]D +57.8°; nmr δ 2.60–3.60 (m, 3, CH_2) 2.75 (s, 3, NCH_3), 4.40 (m, 1, CH), 6.07–6.70 (m, 5, aromatic), 8.72 (b, 3, 3 OH), 8.92 (s, 1, OH), 9.90 (b, 1, N^+H); uv_{max} 230 nm (ε 11,200) (infl), 286 (6600); ORD (*c* 0.364, MeOH) $[\phi]_{600}$ +212°, $[\phi]_{589}$ +223°, $[\phi]_{299}$ +5510° (pk), $[\phi]_{283}$ −6300° (tr), $[\phi]_{244}$ +8925° (pk), and $[\phi]_{228}$ −10,500° (tr); CD (*c* 0.0095 *M*, MeOH) $[\theta]_{310}$ 0, $[\theta]_{292}$ +8610, $[\theta]_{258}$ +840, $[\theta]_{237}$ +19,110, $[\theta]_{222}$ +9240, $[\theta]_{212}$ +40,950, and $[\theta]_{220}$ +13,600. *Anal.* ($C_{17}H_{19}NO_4$·HBr·0.5H_2O) C, H, N.

(−)-(1*R*)-1-(3,4-Dihydroxybenzyl)-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide Hemihydrate [(*R*)-(−)-Laudanosoline Hydrobromide] (4d·HBr). Reductive methylation of 4a afforded 75% of (*R*)-(−)-laudanosine (4c): mp 84–85°; [α]D −107.0° (EtOH) [lit.[17] mp 89°, [α]D −106° (EtOH)]. By the procedure given for the preparation of 1d·HBr, O-demethylation of 4c afforded 70% of 4d·HBr: mp 124–125°; [α]D −57.3°; identical in nmr and uv with 3d·HBr; ORD and CD mirror images of 3d·HBr. *Anal.* ($C_{17}H_{19}NO_4$·HBr·0.5H_2O) C, H, N.

Conversion of (*S*)-(−)-Tetrahydropapaveroline Hydrochloride (3b·HCl) into (*S*)-(+)-Laudanosine (3c). A suspension of 500 mg (1.55 mmoles) of 3b·HCl in 30 ml of MeOH was treated with CH_2N_2 according to the procedure given for the conversion of 1b into 1c to afford, after crystallization from ether, 350 mg (55%) of 3c, identical in mmp, [α]D and nmr with 3c obtained from 3a.

Acknowledgments. We wish to thank the following members of our Physical Chemistry Department (Director, Dr. R. P. W. Scott): Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the nmr spectra, and Dr. V. Toome for the uv, ORD, and CD spectra.

References

(1) A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, **55**, 15 (1972) (paper 1).
(2) P. Holtz, K. Stock, and E. Westermann, *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.*, **248**, 387 (1964).
(3) P. V. Halushka and P. C. Hoffmann, *Biochem. Pharmacol.*, 17, 1873 (1968).
(4) V. E. Davis and M. S. Walsh, *Science*, **167**, 1005 (1970).
(5) H. Yamanaka, M. S. Walsh, and V. E. Davis, *Nature (London)*, **227**, 1143 (1970).
(6) G. Cohen and M. Collins, *Science*, 167, 1749 (1970).
(7) T. L. Sourkes, *Nature (London)*, **229**, 413 (1970).
(8) R. Heikkila, G. Cohen, and D. Dembiec, *J. Pharmacol. Exp. Ther.*, 179, 250 (1971).
(9) A. M. Hjort, E. J. deBeer, and R. W. Fassett, *ibid.*, **62**, 195 (1938); D. W. Fassett and A. M. Hjort, *ibid.*, **63**, 253 (1938); A. M. Hjort, E. J. deBeer, J. S. Buck, and L. O. Randall, *ibid.*, **76**, 263 (1942).
(10) A. H. Beckett, *Fortschr. Arzneimittelforsch.*, 1, 455 (1959).
(11) E. Späth, and F. Dengel, *Chem. Ber.*, **71**, 113 (1938).
(12) A. R. Battersby and T. P. Edwards, *J. Chem. Soc.*, 1214 (1960).
(13) A. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Ramuz, *ibid.*, 3600 (1964).
(14) K. Kakemi, *Yakugaku Zasshi*, **60**, 11 (1940).
(15) T. Reichstein and A. Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934).
(16) H. Corrodi and E. Hardegger, *ibid.*, **39**, 889 (1956).
(17) A. Pictet and B. Athanesecu, *Chem. Ber.*, **33**, 2346 (1900).

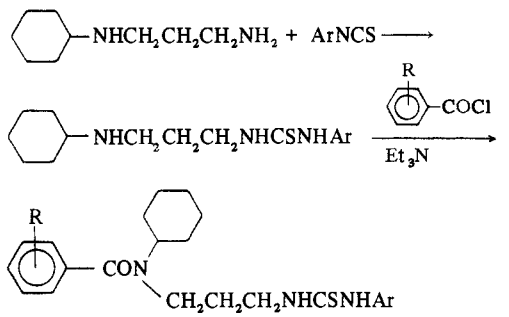
Anticonvulsant Activity of Nitrobenzamides and Their Inhibition of Nicotinamide-Adenine Dinucleotide Dependent Oxidations†

Surendra S. Parmar,* C. Dwivedi,‡ Basheer Ali,§ and R. S. Misra§

Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow-3, India.
Received January 5, 1972

CNS-depressant properties exhibited by *N*-cyclohexylnitrobenzamides[1-3] prompted the synthesis of *N*-cyclohexyl-*N*-(1-aryl-3-propylthiocarbamido)nitrobenzamides. Anticonvulsant properties of these nitrobenzamides were investigated against pentylenetetrazol-induced seizures. Selective inhibitory effects of these nitrobenzamides were observed on nicotinamide-adenine dinucleotide (NAD) dependent oxidation of pyruvate, α-ketoglutarate, β-hydroxybutyrate, and $NADH_2$ where NAD-independent oxidation of succinate was unaltered. Attempts were made to correlate the anticonvulsant activity of these nitrobenzamides with their enzyme inhibitory properties. The various nitrobenzamides were synthesized according to steps outlined in Scheme I.

Scheme 1



Experimental Section

1-Aryl-3-(3-cyclohexylaminopropyl)thiocarbamides. 3-Cyclohexylaminopropylamine (0.02 mole) and suitable aryl isothiocyanates (0.02 mole) were mixed in 30 ml of dry PhH and warmed on a steam bath for 30 min. The reaction mixt was concd under reduced pressure. On cooling, the solid mass which sepd out was filtered, washed (H_2O, Et_2O), dried, and recrystd (EtOH). All compounds were characterized by their sharp melting points and elemental analyses (Table I).

***N*-Cyclohexyl-*N*-(1-aryl-3-propylthiocarbamido)nitrobenzamides.** Following the method of Roll[3] to a well-stirred and cooled mixt of 1-aryl-3-(3-cyclohexylaminopropyl)thiocarbamide (0.005 mole) and $(Et)_3N$ (0.005 mole) in 20 ml of DMF, an appropriate nitrobenzoyl chloride (0.005 mole) soln in 10 ml of DMF was added, and the mixt was stirred for 30 min. The crude product, which sepd out by the addition of ice water, was filtered, washed (H_2O), dried, and recrystd (EtOH-H_2O). These nitrobenzamides were characterized by their sharp melting points and elemental analyses (Table II).

Biochemical Studies. Materials and Methods. Commercial chemicals were used in the present study. AMP, cytochrome *c*, α-ketoglutarate, and $NADH_2$ were obtained from Sigma Chemical Co., St. Louis, Mo., sodium β-hydroxybutyrate from Mann Research Laboratories Inc., New York, N. Y., sodium pyruvate from E. Merck, Darmstadt, and sodium succinate and other common chemicals were purchased from the British Drug House, Bombay.

Assay of Respiratory Activity of Rat Brain Homogenate. Res-

†This investigation was supported in part by financial assistance obtained from the Indian Council of Medical Research, New Delhi, and the Council of Scientific and Industrial Research, New Delhi.
‡Junior Research Fellow of I.C.M.R., New Delhi.
§Junior Research Fellow of C.S.I.R., New Delhi.