New Compounds: Synthesis of Alkyl Esters of D,L-Dopa

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Abstract □ In the search for possible prodrugs of levodopa, seven alkyl esters of D,L-dopa were prepared using thionyl chloride as the catalyst. The hydrochloride salts were quite stable to hydrolysis in acidic aqueous solutions.

Keyphrases □ D,L-Dopa—synthesis of alkyl esters □ Levodopa—synthesis of alkyl esters of D,L-dopa as a possible prodrug

Extensive clinical trials undertaken during the last decade have shown that levodopa (L-3,4-dihydroxyphenylalanine) is frequently an effective drug in the treatment of Parkinsonism (1–5). It is generally accepted that orally administered levodopa is absorbed into the blood, passes the blood–brain barrier, and is converted to dopamine in the brain. The resulting increase in brain dopamine and related catecholamines is believed responsible for the effectiveness of the drug in treating Parkinsonism. Although levodopa is now considered the drug of choice, there are still problems associated with its use. A significant number of patients do not respond to treatment, while many who do respond require very large doses and often suffer undesired side effects. A recent report indicated (6) the therapeutic response to levodopa depends on the efficiency of absorption and the attainment of adequate blood levels.

Other workers have also studied the biopharmaceutic and pharmacokinetic aspects of this drug. Peaston and Bianchine (7) measured the total radioactivity in the blood of 22 patients after oral doses of ^{14}C-labeled levodopa and found the ^{14}C to be rapidly and almost completely absorbed. Subsequently, three other laboratories reported studies in which levodopa in the blood was measured following oral administration of the drug (8–10). These studies showed that only about 20–30% of the orally administered dose reached the general circulation as the intact drug and suggested that the remainder is biotransformed in the GI tract and/or the liver during its "first passage" to the general circulation. These results are not surprising when the number of degradative reactions to which levodopa is subject is considered (11–14). One possible method for improving the absorption of levodopa and/or making it less labile could be the administration of a prodrug which can be transformed to the active drug following absorption. In this laboratory the use of alkyl esters as possible prodrugs for levodopa is currently under investigation. The preparation of seven esters of the less expensive D,L-dopa is reported in this article.

Table I—Alkyl Ester Hydrochlorides of D,L-Dopa

Ester	Melting Point	Yield, %	Analysis[a], % Calc.	Analysis[a], % Found	Spectral Data: IR[b] Max. cm.$^{-1}$	Spectral Data: UV[c] Max., nm.	Spectral Data: UV[c] ϵ	Spectral Data: Half Bandwidth, nm.
Methyl	179–180°	73.96	C 48.49 H 5.70 N 5.65	48.10 6.08 5.35	3370; 2940 1724 1205–1290 775– 826	280	2635	22.0
n-Propyl	179°	88.20	C 52.27 H 6.58 N 5.08	52.39 6.68 5.01	3370; 2970 1735 1205–1300 780– 825	280	2865	23.0
Isopropyl	198–199°	63.41	C 52.27 H 6.58 N 5.08	51.99 6.62 5.05	3370; 2950 1724 1200–1300 780– 830	280	2845	23.0
n-Butyl	180–181°	81.66	C 53.89 H 6.96 N 4.83	54.07 7.02 4.82	3370; 2950 1730 1200–1300 780– 825	280	2900	22.5
Isobutyl	217–218°	94.76	C 53.89 H 6.95 N 4.83	54.01 7.01 4.84	3350; 2950 1730 1200–1300 780– 825	280	2845	22.5
n-Pentyl	185–186°	91.74	C 55.35 H 7.30 N 4.61	54.98 7.56 4.58	3360; 2940 1730 1200–1300 780– 825	280	2840	23.0
Isoamyl	197–198°	82.92	C 55.35 H 7.30 N 4.61	55.19 7.34 4.63	3370; 2950 1730 1200–1300 780– 880	280	2795	23.0

[a] Analyses were performed by Atlantic Microlab, Inc. [b] I in KBr pellets. [c] UV absorption spectra of 2×10^{-4} *M* solution in 0.1 *N* HCl.

EXPERIMENTAL[1]

Materials—The D,L-dopa used was 3,4-dihydroxyphenylalanine[2], which decomposed between 270 and 272° and was employed without further purification. All other reagents were of the highest quality commercially available and were used without further purification.

Preparation of the Alkyl Ester Hydrochlorides of Dopa—A modification of the procedure presented by Patel and Price (15), in which thionyl chloride acts as the catalyst, was used to prepare seven alkyl esters of D,L-dopa. One hundred milliliters of the appropriate alcohol was placed in a 200-ml. three-necked flask, which was equipped with a reflux condenser and a tube for nitrogen bubbling. The alcohol was cooled to from −5 to −10° and sparged with nitrogen for 10 min. The thionyl chloride (15 ml.) was added slowly over 15 min., and the reaction mixture was stirred for an additional 15 min. After stirring, 4 g. of D,L-dopa was added, the temperature was adjusted to 40°, and the mixture was refluxed for 12 hr. The hydrochloride salts of the isobutyl, pentyl, and isoamyl esters precipitated directly from the reaction solution. The other four ester hydrochlorides were precipitated by adding just enough petroleum ether to make the solution turbid and then placing them in the refrigerator for a few hours. All of the products were collected by filtration and were recrystallized from an absolute alcohol–ether mixture. The crystals were dried in a vacuum desiccator at room temperature and stored in the desiccator until used. For each ester hydrochloride of D,L-dopa, the melting point, IR and UV spectra, and microanalysis data are presented in Table I. The Arnow (16) test for catechol was positive for each ester.

Paper Chromatography—A paper chromatographic method for the qualitative analysis of D,L-dopa in solutions containing one or more of the alkyl esters of dopa was developed. A solvent system consisting of *n*-butanol–water–acetic acid (16:7:1) was found to effect a separation of the amino acid from the various esters when sample solutions were spotted on Whatman No. 1 paper and developed in an ascending manner. The location of the compounds on the developed chromatograms was determined by exposing the paper to ammonia vapors and observing the brown-yellow color develop as they were oxidized. For duplicate runs on solutions of D,L-dopa with each of the seven esters, the R_f value for dopa was between 0.17 and 0.19, while the esters ranged between 0.30 for the methyl ester and 0.85 for the *n*-butyl ester. The possible hydrolysis at 37° of 1 m*M* solutions of each of the seven esters buffered[3] at pH 1, 3, and 5 was evaluated using the paper chromatographic method. No hydrolysis was detected for up to 12 hr.

[1] All IR spectra were obtained with a Perkin-Elmer 237 B grating spectrophotometer. The UV spectra and analyses were obtained with Perkin-Elmer 202 and Beckman DU spectrophotometers, respectively. The melting points were determined on a Thomas-Hoover capillary melting-point apparatus.

[2] White Label, Nutritional Biochemical Corp.

[3] Using 0.2 *M* HCl and acetate buffers.

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