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Note

Increasing the optical rotation of L-carbidopa by reaction with dicarbonyl compounds

Steven H. Neau, Lester Chafetz and Michelle Y. Chow

Center for Pharmaceutical Technology, University of Missouri-Kansas City, School of Pharmacy, Kansas City, MO 64110-2499 (U.S.A.)

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Summary

To enhance optical rotation, the hydrazino moiety of L-carbidopa was derivatized to a pyrazole ring by reaction with a β-dicarbonyl compound, 2,4-pentanedione, 1,1,1-trifluoro-2,4-pentanedione or malondialdehyde. Reaction with 2,4-pentanedione produced a product with an increased specific rotation in a derivatization completed in 20 min.

L-Carbidopa (*S*-(−)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid monohydrate) is reported to have a specific rotation of −17.3° in methanol. Both the United States and British Pharmacopeia make use of the chelation of L-carbidopa with aluminum, using aqueous aluminum chloride as the solvent in a polarimetric analysis. This provides a negligible increase in optical rotation. Under these conditions, the USP requirement is a specific rotation, $[\alpha]_D$, between −21 and −23.5° at 25°C, and the BP requires between −22.5 and −26.5° measured at 20°C, the difference being due to the temperature of the measurement. Ceccarini and Maione (1987) proposed measurement at 25°C using a 3.05% solution in a mixture of equal volumes of concentrated formic and acetic acids containing *p*-dimethylaminobenzaldehyde. Hydrazone formation under these conditions was completed in 10 min. The derivative exhibited a specific rotation of about +190°, and observed rotations are linear from 0.6 to 3% (w/v). Although this proposal has merit, we have reservations on the use of the corrosive acids.

Dee (1971) determined hydrazine and methylhydrazine by gas chromatography, using 2,4-pentanedione to make the corresponding pyrazoles. The reaction was completed within 1 h over the pH range of 6–9. Because the catechol function is unstable in this pH range, we studied the reaction of the hydrazino moiety of L-carbidopa with β-dicarbonyl compounds only under acidic conditions (see Fig. 1). Pyrazole derivatization of L-carbidopa was studied at various acid pH values using 2,4-pentanedione, 1,1,1-trifluoro-2,4-pentanedione or

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Correspondence: S.H. Neau, Center for Pharmaceutical Technology, University of Missouri-Kansas City, School of Pharmacy, Kansas City, MO 64110-2499, U.S.A.

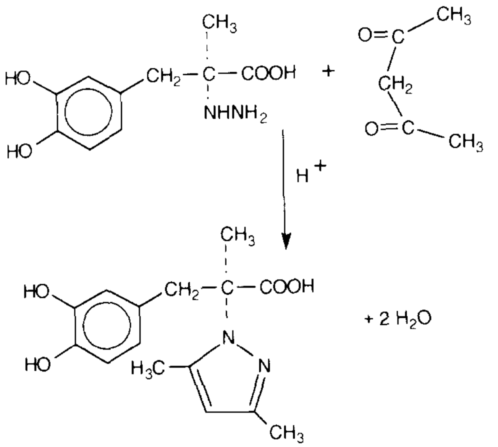

Fig. 1. Reaction of L-carbidopa with 2,4-pentanedione to form a pyrazole with enhanced optical rotation.

the tetraethoxy acetal of malondialdehyde. Solution discoloration was encountered using malondialdehyde in acid, possibly due to aldol reactions. The trifluoro dicarbonyl gave a larger increase in observed rotation; however, its reaction rate was slower than that of 2,4-pentanedione.

Chafetz (1991) proposed changing the wavelength for measurement of optical rotation from the sodium D-line (589 nm) to the lower wavelengths afforded by isolating the lines from a mercury lamp with the use of a photoelectric polarimeter. Such instruments are nearly ubiquitous in pharmaceutical laboratories, their precision is much better than that of visual polarimeters, mercury lamps last twice as long as sodium arc lamps and the rotations at 365 nm are generally 3 times greater than at 589 nm.

The recommended procedure is simple: dissolve 40 mg (0.16 mmol) of L-carbidopa in about 9 ml of 1 N hydrochloric acid in a 10 ml volumetric flask. Add 320 μl (3.1 mmol) of 2,4-pentanedione, bring to the mark with hydrochloric acid and mix well. Allow to stand for 20 min and determine the optical rotation of the solution in a 1 dm polarimeter cell using the 365 nm wavelength. The first-order reaction rate for disappearance of L-carbidopa was about 0.34 min^{-1} at 25°C. The specific rotation, $[\alpha]_{365}$, at 25°C was about $-139°$, and the relation between observed rotation and concentration was linear from 0.1 to 1.0% (w/v) of L-carbidopa. The derivative exhibiting the increased optical rotation is presumed to be *S*-(−)-3-(3,4-dihydroxyphenyl)-2-(3,5-dimethylpyrazolo)-2-methylpropanoic acid.

References

Ceccarini, G. and Maione, A.M., Optical rotation enhancement of L-carbidopa by reaction with aromatic aldehydes. *J. Pharm. Sci.*, 76 (1987) 851–852.

Chafetz, L., Optical rotation and drug standards. *Pharm. Technol.*, 15 (1991) 52–61.

Dee, L.A., Gas Chromatographic determination of aqueous trace hydrazine and methylhydrazine as corresponding pyrazoles. *Anal. Chem.*, 43 (1971) 1416–1419.