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Synthesis of L-Dopa (3,4-Dihydroxyphenyl-L-alanine)

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N-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine (L-I) and *N*-acetyl-3-(3,4-methylenedioxyphenyl)-L-alanine (L-II) could be starting materials for the synthesis of L-dopa. A new chemical resolution method of *N*-acetyl-3-(3,4-dimethoxyphenyl)-DL-alanine (I) and *N*-acetyl-3-(3,4-methylenedioxyphenyl)-DL-alanine (II) by using *d*-ephedrine as a resolving reagent was adopted.

Experimental Section

***N*-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine-*d*-ephedrine Salt (*d*-Ephedrine-L-I Salt).**—*N*-Acetyl-3-(3,4-dimethoxyphenyl)-DL-alanine (DL-I) (53.4 g, 0.2 mole) and 33.0 g of *d*-ephedrine (0.2 mole) were dissd together in 130 ml of MeOH or in 200 ml of EtOH with warming at 55–60° for 1.0 hr, and the soln was kept in a refrigerator overnight. The colorless crystals that sepd were filtered off, washed with MeOH (ca. 30 ml), and dried, giving 37.9 g (87.8%) of the *d*-ephedrine-L-I salt: mp 147.5–149.5°, $[\alpha]^{20}_D + 49.8^\circ$ (c 5, H₂O). After recrystn from 3 vol of MeOH, the mp and $[\alpha]_D$ became constant: mp 152–153°; $[\alpha]^{20}_D + 54.5^\circ$ (c 5, H₂O); yield, 28.4 g (68.1%). *Anal.* (C₂₃H₃₂N₂O₆) C, H, N.

***N*-Acetyl-3-(3,4-methylenedioxyphenyl)-L-alanine-*d*-ephedrine Salt (*d*-Ephedrine-L-II Salt).**—DL-II (90.4 g) and *d*-ephedrine (72.7 g) were dissd in 600 ml of MeOH or 900 ml of EtOH at 55–60° with stirring for 1.0 hr, cooled, and kept in a refrigerator overnight. The colorless crystals that sepd were filtered off, washed with MeOH (ca. 30 ml), and dried, giving 66.5 g (89.1%) of the *d*-ephedrine-L-II salt: mp 150.2–152.5°; $[\alpha]^{20}_D + 48.2^\circ$ (c 5, H₂O). Recrystn from 3 vol of MeOH gave 46.6 g (62.1%) of *d*-ephedrine-L-II: mp 156.3–158.6°; $[\alpha]^{20}_D + 55.6^\circ$ (c 5, H₂O). *Anal.* (C₂₂H₂₈N₂O₆) C, H, N.

***N*-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine (L-I) from the *d*-Ephedrine-L-I Salt.**—*d*-Ephedrine-L-I (20 g) was dissd in 50 ml of H₂O, then this soln was added dropwise with 30% HCl with cooling and stirring, giving colorless crystals. After standing in a refrigerator overnight they were filtered off, washed with H₂O (20 ml), and dried, affording 11.4 g (91.0%) of L-I: mp 149–150°; $[\alpha]^{20}_D + 46.2^\circ$ (c 5, MeOH). *Anal.* (C₁₃H₁₇NO₅) C, H, N.

***N*-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine (L-I) from the *d*-Ephedrine-L-I Salt.**—*d*-Ephedrine-L-I (20 g) was dissd in 50 ml of H₂O, then this soln was added dropwise with 20% HCl with cooling and stirring, giving colorless crystals. After standing in a refrigerator overnight they were filtered off, washed with H₂O (20 ml), and dried, affording 11.4 g (91.0%) of L-I: mp 149–150°; $[\alpha]^{20}_D + 46.2^\circ$ (c 5, MeOH). *Anal.* (C₁₃H₁₇NO₅) C, H, N. From the filtrate and washings of the acid (L-I), *d*-ephedrine-HCl was nearly quant recovered as colorless crystals; mp 217–218°; $[\alpha]^{20}_D + 34.1^\circ$ (c 1, H₂O).

***N*-Acetyl-3-(3,4-methylenedioxyphenyl)-L-alanine (L-II) from the *d*-Ephedrine-L-II Salt.**—*d*-Ephedrine-L-II salt (58.8 g) was dissd in 150 ml of H₂O and added dropwise to 20% HCl under cooling and stirring, giving colorless crystals. After standing in a refrigerator overnight they were filtered off, washed with 50 ml of cold H₂O, and dried, affording 33.7 g (95.0%) of L-II based on the

L-II of *d*-ephedrine-L-II used: mp 179.6–180.8°; $[\alpha]^{20}_D + 46.5^\circ$ (c 5, MeOH). *Anal.* (C₁₂H₁₃NO₅) C, H, N.

L-Dopa (L-III) from L-I.—A mixt of 26.8 g (0.1 mole) of L-I, 69.8 ml (0.6 mole) of 47% HBr, and 28 ml (0.32 mole) of PhOH was heated under stirring and reflux for 6 hr, and the resulting slight brown soln was evapd to a reddish syrup. This was dissd in 30 ml of *n*-BuOAc and extd twice with 30 ml and 10 ml of H₂O. The 2 aq exts were combined and adjusted to pH 5.0 with 25% NH₄OH soln contg a little NaHSO₃, whereupon colorless crystals sepd. After standing in a refrigerator overnight the crystals were filtered off, washed with H₂O, and dried, giving 19.6 g (99.5%) of crude L-dopa: mp 266–269°; $[\alpha]^{15}_D - 11.6^\circ$ (c 5, 1 N HCl). Recrystn from 800 ml of H₂O contg a little NaHSO₃ gave 15.6 g (79.5%) of L-dopa as colorless minute leaflets: mp 277–278° dec; $[\alpha]^{15}_D - 13.3^\circ$ (c 5, N-HCl). *Anal.* (C₉H₁₁NO₄) C, H, N.

L-Dopa from L-II.—L-II (30 g) and PhOH (30 g) were heated in 300 ml of 20% HCl under reflux and stirring for 20.0 hr, and the resulting soln was evaporated to the reddish syrup. This was worked up as in the preceding expt: yield, 22.6 g (95.6%); mp 268–270°, $[\alpha]^{17}_D - 11.8^\circ$ (c 5, N-HCl); after recrystn 16.4 g (82.0%) of L-dopa, mp 277.2–278.2° dec, $[\alpha]^{15}_D - 13.2^\circ$ (c 5, 1 N HCl). *Anal.* (C₉H₁₁NO₄) C, H, N.

Evaluation of Carbazoles as Antifungal Agents

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Some complex carbazole alkaloids have been reported to possess antifungal activity.¹ In a search for similar agents, a group of simple derivatives were prepared² and evaluated against *Candida albicans*.³ None of the results are sufficiently high to recommend these compounds for further testing.

TABLE I
ANTI-*Candida* ACTIVITY

No.	Carbazole ^a	Concn, mg/ml	Activity zone size, mm ^b
1	1-OH	0.1	12
2	1-OH-3-Me	0.1	11
3	3-MeO-6-Me	0.1	12
4	1,3-(MeO) ₂ -6-Me	0.1	11
5	2,3-(MeO) ₂ -6-Me	0.1	11
6	2,4-(MeO) ₂ -6-Me	1.0	c
7	2,3-(OH) ₂ -6-Me	0.1	10
8	<i>N</i> -Me-2,3-(MeO) ₂ -6-Me	1.0	c
9	Glycozolidine ^d	1.0	c

^a All new compds had satisfactory anal. (C, H, N) and spectral values. ^b In an agar diffusion cup-plate assay, where the cup diameter itself is 8 mm. ^c The zone was not larger than that produced by the diluent (ethylene glycol-EtOH, 4:1). ^d D. P. Chakraborty and B. P. Das, *Sci. Cult.*, **32**, 181 (1966).

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(1) K. C. Das, D. P. Chakraborty, and P. K. Bose, *Experientia*, **21**, 340 (1965).

(2) K. C. Das and B. Weinstein, unpublished data.

(3) We thank Dr. John W. Westley, Hoffman-LaRoche, Nutley, N. J., for furnishing the test report.