EXPERIMENTAL[1]

One-tenth mole of anil in 50 ml. of methanol was reduced with 0.15 mole (5.6 g.) of sodium borohydride (2). The mixture was refluxed for 30 min., the methanol was removed by distillation, 50 ml. of water was added, and the mixture was cooled. The oily reaction mixture was then extracted twice with 50-ml. portions of ether. The extracts were combined, dried over anhydrous calcium sulfate, and acidified with anhydrous hydrogen chloride. The crystals were collected, washed with dry ether, and recrystallized from an ethanol–ether mixture.

[1] All melting points were taken on a Thermalyne apparatus and were not corrected.

REFERENCES

(1) H. A. Luts, *J. Pharm. Sci.*, **60**, 1903(1971).

(2) H. A. Luts, W. Zucarello, and J. F. Grattan, *ibid.*, **54**, 460 (1965).

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▲ To whom inquiries should be directed. Present address: Eastern Kentucky University, Richmond, KY 40475

New Compounds: Resolution of *d,l*-α-Benzamido-4-hydroxy-3-methoxydihydrocinnamic Acid, a Precursor of *l*-3,4-Dihydroxyphenylalanine

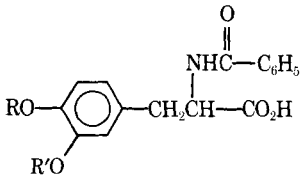
THOMAS J. SCHWAN▲ and HOMER A. BURCH

Abstract □ *d,l*-α-Benzamido-4-hydroxy-3-methoxydihydrocinnamic acid was resolved using dehydroabietylamine, and the *l*-salt thus obtained was converted to *l*-3,4-dihydroxyphenylalanine.

Keyphrases □ *d,l*-α-Benzamido-4-hydroxy-3-methoxydihydrocinnamic acid—resolution using dehydroabietylamine □ *l*-3,4-Dihydroxyphenylalanine—resolution of a precursor, *d,l*-α-benzamido-4-hydroxy-3-methoxydihydrocinnamic acid, using dehydroabietylamine □ Dehydroabietylamine—used to resolve *d,l*-α-benzamido-4-hydroxy-3-methoxydihydrocinnamic acid, a precursor of *l*-3,4-dihydroxyphenylalanine

The recent interest in *l*-3,4-dihydroxyphenylalanine (I) for the treatment of Parkinson's disease prompted an investigation into the synthesis of this amino acid. Although *d,l*-α-benzamido-3-hydroxy-4-methoxydihydrocinnamic acid (II) had been resolved using cinchonine (1), resolution of the isomeric amino acid III, derived from vanillin in the azlactone synthesis, apparently had not been previously reported[1].

Resolution of III was not achieved with cinchonine but was readily effected in excellent yield in the present work with dehydroabietylamine (IV). The optically active amine IV, previously isolated from commercial Amine D, is a relatively inexpensive, nontoxic agent and has been employed in the resolution of racemic α-phenoxypropionic acid and racemic α-benzyloxycarbonylaminophenylacetic acid (2).



II: R = CH_3, R′ = H
III: R = H, R′ = CH_3

Treatment of the resolved *l*-salt of III with dilute hydrochloric acid followed by refluxing 48% HBr yielded I. Thus, this resolution of racemic II afforded I in high optical purity and good yield without lengthy fractional crystallization.

EXPERIMENTAL[2]

Resolution of *d,l*-α-Benzamido-4-hydroxy-3-methoxydihydrocinnamic Acid (III)—Dehydroabietylamine (IV) (57 g., 0.20 mole) was dissolved in 450 ml. boiling methanol, and a small amount of mechanical impurity was removed by filtration. The solution was heated to boiling, and a solution of III (3) (63 g., 0.20 mole) in 160 ml. boiling methanol was added. The solution was boiled, and 113 ml. of boiling water was added (to turbidity). The mixture was allowed to cool gradually to room temperature and was stored at room temperature for 18 hr. The product was washed with two 125-ml. portions of methanol–water (4:1), air dried, and then dried at 60° to give 51 g. (83%) of the product, m.p. 223–224°; $[\alpha]_D^{25}$ +50.30° (concentration 1.91%, methanol). The analytical sample was obtained after three recrystallizations from methanol–water (4:1); $[\alpha]_D^{25°}$ +53.50° (concentration 1.97%, methanol).

Anal.—Calc. for $C_{17}H_{17}NO_5 \cdot C_{20}H_{31}N$: C, 73.87; H, 8.44; N, 4.66. Found: C, 73.97; H, 8.05; N, 4.66.

***l*-3,4-Dihydroxyphenylalanine (I)**—A 3-ml. portion of concentrated hydrochloric acid was added to a mixture of 3.85 g. (0.0064 mole) of the resolved salt of IV and III, 40 ml. water, and 40 ml. ethyl acetate. The organic layer was separated, and the aqueous

[1] After this work was completed, resolution of III using dehydroabietylamine was reported; A. Kaiser, M. Scheer, W. Haeusermann, and L. Marti, German pat. 1,964,420; through *Chem. Abstr.*, 74, 3864y (1971).

[2] Melting points were taken in a Mel-Temp apparatus in open capillary tubes and are uncorrected. The optical rotation measurements were determined on a Perkin-Elmer 141 polarimeter. The amino acid analysis was conducted on a Phoenix Precision Instruments amino acid analyzer, using a 50-cm. 2-Å column at 50° and pH 5.29, with Pierce *d,l*-3,4-dihydroxyphenylamine, Puriss. grade, employed as the standard.

layer was extracted with two 40-ml. portions of ethyl acetate. The combined organic layers were washed with 50 ml. water, dried (magnesium sulfate), and concentrated to dryness *in vacuo* to give 3.10 g. of the acid. To the acid was added 50 ml. 48% HBr. The mixture was stirred and refluxed for 2.25 hr. and then allowed to stand at room temperature for 15 hr. The solid was filtered and washed with two 5-ml. portions of 48% HBr. The fitrate and washings were combined and concentrated to dryness *in vacuo*. To the residue was added 10 ml. water and a few drops of sulfur dioxide–water. The solution was warmed, decolorized, and filtered. The filtrate was cooled, adjusted to pH 5 (pH paper) with concentrated ammonium hydroxide, and stored in the refrigerator for 2 days. The solid was filtered, washed with two 10-ml. portions of absolute ethanol, and air dried to give 0.52 g. (40%) of I; $[\alpha]_D^{25°}$ −11.15° (concentration 2%, 1 *N* HCl). An analytically pure sample of I was isolated from velvet bean extract by the literature method (4); $[\alpha]_D^{25°}$ (obs.): −11.62° (concentration 2%, 1 *N* HCl), (lit.): −12.0° (concentration 1%, 4% HCl). The product exhibited an IR spectrum identical to that of an authentic sample of I. Amino acid analysis indicated the purity of the product to be 97%.

REFERENCES

(1) K. Vogler and H. Baumgartner, *Helv. Chim. Acta*, **35**, 1776 (1952).

(2) W. J. Gottstein and L. C. Cheney, *J. Org. Chem.*, **30**, 2072 (1965).

(3) Y. Sugii, *J. Pharm. Soc. Japan*, **468**, 130(1921); through *Chem. Abstr.*, **15**, 22818(1921).

(4) R. R. Sealock, in "Biochemical Preparations," vol. I, H. E. Carter, Ed., Wiley, New York, N. Y., 1949, pp. 25–27.

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COMMUNICATIONS

Existence of a Vagosympathetic Pressor Reflex in the Dog

Keyphrases ☐ Central vagal stimulation—vagosympathetic pressor reflex, dogs ☐ Vagosympathetic pressor reflex—response to central vagal stimulation, sympathetic efferents *versus* vagal afferents, dogs

Sir:

It has been substantiated by many workers, among whom may be mentioned Chapman *et al.* (1) and Tansy *et al.* (2), that central vagal stimulation at the cervical level in the bilaterally vagectomized dog invariably produces a definite and constant elevation in arterial pressure with no change in the pulse rate or ECG.

From these reports it was to be assumed that the pressor response to central vagal stimulation in the dog results from vagal afferent activity. In a recent report, Pedersoli (3) concluded, however, that the pressor response was mediated solely by simultaneous stimulation of the sympathetic fibers which are fused into the common trunk with the vagus nerve in the cervical region of the dog. We, therefore, subjected this question to further examination.

Acute experiments were conducted in 12 fasted mongrel dogs to determine the afferent pathway which subserves the arterial pressor response to central stimulation of the vagosympathetic trunk. After an overnight fast, anesthesia was induced with sodium thiopental (20 mg./kg. body weight) and maintained with a mixture of chloralose–urethan (25 and 250 mg./kg. body weight, respectively). In all preparations, the vagus was surgically separated from its sympathetic component by locating the superior cervical ganglion and dividing the common sheath holding together the sympathetic efferent nerves and the vagus. The dissected right and left vagosympathetic trunks were sectioned in the neck and prepared for cephalad stimulation as described by Taylor and Page (4).

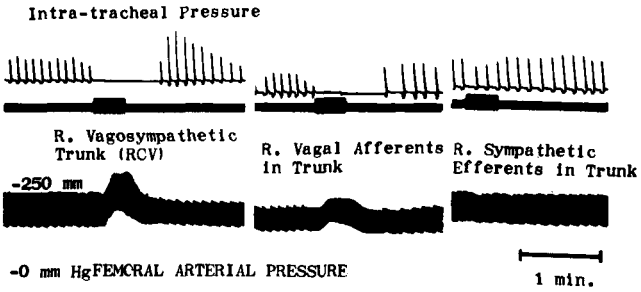

Figure 1—*Polygram sections showing arterial pressure and respiratory responses to electrical stimulation of the cut cephalic end of the entire right vagosympathetic trunk of the dog, the vagal portion of the same trunk, and the peripheral sympathetic component.*

The cephalic end of the divided vagosympathetic trunk, its vagal afferent, and sympathetic efferent components were stimulated with monophasic square wave pulses, using pressor parameters described by Feldman (5). The stimuli consisted of monophasic square wave pulses, with a frequency range of 30–60 Hz., a duration of 1 msec., and voltages of 10–40 v. Absolute current flow was measured using voltage drop determination across a precision resistor of known value in series with