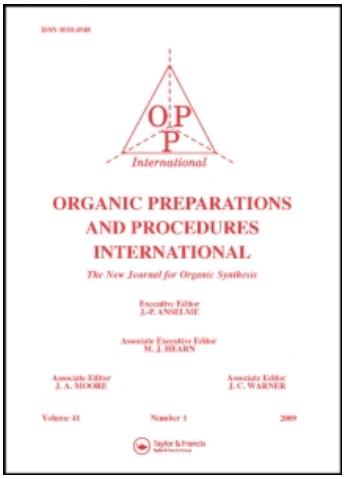

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NOVEL CYANOHYDRIN FORMATION AND ISOLATION IN THE SYNTHESIS OF 5-IODONOREPINEPHRINE

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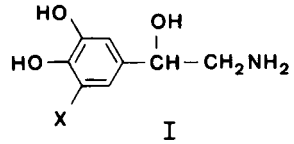
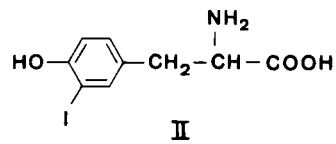
The synthesis of the three monofluoro-substituted norepinephrines and their altered adrenergic activities as compared to that of norepinephrine (Ia) itself have been reported.[1] The enhanced β-adrenergic activity of 5-fluoronorepinephrine (Ib) was particularly noteworthy because the halogen substituent in that compound occupies a position analogous to that of iodine in the aromatic amino acid 3-iodotyrosine (II) and in the outer



I

a) X = H b) X = F

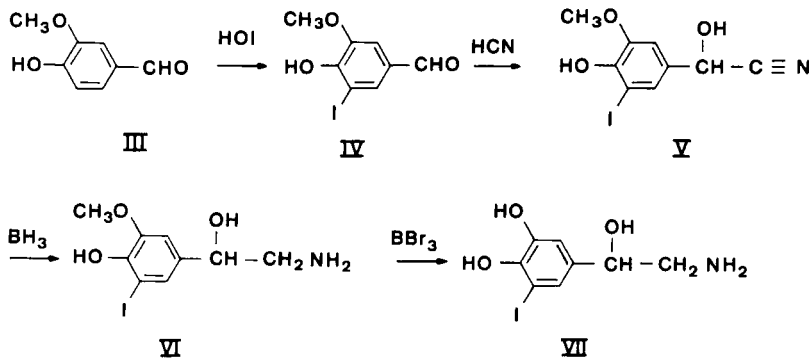


II

ring of the amino acid hormone, 3,3',5-triiodothyronine. Compound II, along with the biosynthetically related thyroid hormones, can be found in every known vertebrate organism. With this in mind, and because theoretical considerations indicate that iodinated analogues of norepinephrine may mediate the β-adrenergic actions of thyroid hormones,[2] the synthesis of 5-iodonorepinephrine (VII) was undertaken in order to test its biological activity and to explore the possibility of its natural occurrence. We now report a method of synthesis of VII as well as ı novel solution to an unexpected problem encountered in this synthesis which may be of general interest.

Hypoiodite iodination of vanillin (III) by the usual procedure[3] gave

5-iodovanillin (IV) for which amplified directions are given below. It was expected that the corresponding cyanohydrin (V) could be generated by reaction of KCN with the bisulfite addition complex of IV. However, all attempts to effect such a synthesis, including methods successful with 5-bromovanillin and the isomeric 5-iodoisovanillin,[4] failed although there was evidence that the desired bisulphite addition complex was formed to a small extent. The method for V which finally evolved was suggested by the direct reaction of certain steroidal carbonyl compounds with HCN generated by the action of glacial acetic acid on potassium or sodium cyanide at or below 0° in ethyl or methyl alcohol.[5] However, in this instance a switch to anhydrous ether as solvent and the maintenance of low temperatures throughout isolation procedures were necessary to obtain the desired product. Additional steps in the synthesis of VII were accomplished through modification of existing procedures.[4,6] The overall synthesis is outlined below and described in detail in the Experimental Section.



We have also prepared intermediate IV by iodination of III with KI and HIO_3 based on the method for iodination of benzoate esters.[7] This method will permit preparation of high specific activity radioiodine-labeled VII using carrier-free radioactive iodide in preparation of IV. Since cyanohydrin V need not be isolated, the overall synthesis of VII can be accomplished in approximately four days with a minimum of handling.

EXPERIMENTAL SECTION

Identities of products were confirmed by chemical ionization mass spectra obtained with a Finnigan mass spectrometer, model 1015D. Melting points (uncorrected) were determined on a Mel-Temp apparatus. NMR spectra were measured with a JEOL model FX100 spectrometer. Spectral and analytical services were provided by the Microanalytical Services and Instrumentation Section of the Laboratory of Chemistry, NIADDK, under the direction of Dr. David F. Johnson.

5-Iodovanillin (IV).- Finely crystalline III (5.32 g, 35 mmol) was added all at once to an iodinating medium[3] consisting of 1 L of borate buffer [21.65 g (350 mmol) of H_3BO_3 in 70 mL of IN NaOH followed by addition of H_2O to volume] and 350 mL of 0.2M KI_3 [70 mmol of I_2 and 22 g of KI in H_2O to volume]. Stirring was continued for 35 min at ambient temperature, unreacted hypoiodite destroyed by addition of 20% $Na_2S_2O_3$ to constant color (~18 mL) and the mixture acidified with 1N H_2SO_4 and placed at 4° overnight to complete separation of product. Before use, crude IV (9.28 g, 95% yield) was recrystallized from glacial acetic acid to give off-white plates, mp. 179-180° (72%). Further recrystallization, unnecessary for the next step, gave prisms, mp. 181-183.5°, lit.[3] mp. 181-182°. NMR($CDC\ell_3$): δ 3.91 (s, 3H, $-OCH_3$), 7.33 (d, 1H, benzene C_2-H, J = 1.5Hz), 7.75 (d, 1H, benzene C_6-H, J = 1.5 Hz), 9.72 (s, 1H, CHO).

In an alternate synthesis of IV, iodic acid (5.86 g, 33 mmol) in 50 mL of H_2O was cautiously added (through the condenser) to a refluxing mixture of vanillin (15.2 g, 100 mmol) and KI (16.6 g, 100 mmol) in ethanol (400 mL), H_2O (50 mL) and 2N acetic acid (140 mL). The dark brown opaque mixture gradually achieved a miximum degree of clarity after 1 hour of refluxing and was refluxed an additional hour before destruction of excess I_2 by addition of $Na_2S_2O_3$ (4 g, in H_2O). Separation of IV as beige crystals began as the mixture cooled and was completed by slow addition of H_2O (600 mL) and chilling. The crystalline product (21.7 g, 78% yield), had a low melting range and retained a strong odor of vanillin.

It was triturated in a solution of 5 g of $NaHSO_3$ in H_2O, filtered, washed with H_2O and dried to yield 18.7 g (66%) of product, mp. 171-177°. This material was shown to be identical with 5-iodovanillin produced by hypoiodite iodination of III, by co-crystallization from glacial acetic acid which gave prisms, mp. 181-183.5°.

5-Iodovanillin cyanohydrin (V).- [Caution! A well-ventilated hood must be used.] Pulverized potassium cyanide (16 g, 246 mmol) was added to a stirred suspension of IV (2.78 g, 10 mmol) in 200 mL of anhydrous diethyl ether and 11.6 mL of glacial acetic acid (203 mmol) while an internal temperature of -5° was maintained. The addition was completed in 15 min after which stirring was continued for 2¼ hours as the temperature rose gradually to 0°. The temperature was raised rapidly to 15°, solids dissolved by addition of sufficient ice chilled H_2O (100 mL) and the resulting layers separated. The aqueous layer was washed twice with ether and the combined ether layer washed twice with 10 mL of H_2O. After brief drying over anhydrous Na_2SO_4, a step which was omitted when V was not actually isolated, the filtered ethereal solution was rapidly concentrated at ambient temperature by rotary evaporation employing a vacuum pump. The resulting slurry was frozen and dried completely by lyophilization. The residue can be used in the next step of the synthesis without further treatment. In order to isolate V, the residue was dissolved in a minimum amount of ether and V was precipitated as a white solid (1.84 g, 60% yield) by addition of hexane (60 mL). Stepwise addition of hexane (20 mL) to a filtered ethereal solution of V (1.59 g in 20 mL) gave an analytically pure material as rosettes of fine white needles, mp. 133-134.5° (70%). Mass spectrometry and NMR confirmed the identity of V.

Anal. Calcd for $C_9H_8INO_3$: C, 35.43; H, 2.64; N, 4.59.

Found: C, 35.60; H, 2.66; N, 4.54

NMR($CDCl_3$, trace D_2O): δ 3.92 (s, 3H, $-OCH_3$), 5.40 (s, 1H, -CH-), 6.99 (d, 1H, benzene C_2-H, J = 1.5Hz), 7.43 (d, 1H, benzene C_6-H, J = 1.5Hz). Mass spectrum (CH_4): 307 ((M-HCN) + $C_2H_5^+$, 5.8%), 306 (M + 1, 7.4%), 279 ((M-HCN) + 1, 100%).

2-Amino-1-(4-hydroxy-3-iodo-5-methoxyphenyl)ethanol (VI)[8].- Solid V obtained from 10 mmol of IV, either as dry lyophilisate (see above) or as isolated crude product, was dissolved in 20 mL of tetrahydrofuran and the solution added dropwise to 1M BH_3 in THF (20 mL, 20 mmol) forming a white, almost solid, matrix. After spontaneous heating subsided, the mixture was refluxed for 1 hour, cooled to 50°, and the solid decomposed by the addition of 3 mL of EtOH. Addition of 50 mL of Et_2O and chilling resulted in separation of VI (yield 60% from IV, ~100% from V). A sample sufficiently pure for the next step was obtained by triturating the crude product in boiling EtOH, chilling, filtering and drying in vacuo, a process which removed H_3BO_3 and completed conversion of an amorphous product into crystalline VI. A suspension of VI in H_2O was dissolved by addition of 1N HCl. Addition of 50% NH_4OH (until just alkaline) caused slow formation of fine white crystals. These were washed with H_2O, dried in vacuo, and subsequently triturated briefly in boiling EtOH before filtering and redrying to give analytically pure VI, mp. 180-181° (dec), with 80% overall recovery from the crude product.

Anal. Calcd for $C_9H_{12}INO_3$: C, 34.97; H, 3.91; N, 4.53.

Found: C, 34.89; H, 4.00; N, 4.49.

NMR(0.2N DCl): δ 3.12 (m, 2H, $-CH_2-$), 4.74 (m, 1H, partially obscured by OH peak, -CH-), 7.22 (d, 1H, benzene C_2-H, J = 1.5Hz), 6.87 (d, 1H, benzene C_6-H, J = 1.5Hz).

5-Iodonorepinephrine (VII).- A suspension of VI (1.54 g, 5.0 mmol) in methylene chloride (30 mL), mechanically stirred under a stream of N_2, was

cooled to -80°. Boron tribromide (5 g, 20 mmol) was added all at once and stirring continued for the next 20 hours as the bath temperature slowly rose. Methylene chloride and excess BBr_3 were removed *in vacuo*, 15 mL of H_2O added at 0° and the resulting mixture stirred under N_2 at room temperature for 18 hours during which time the mixture clarified. It was extracted with ether, the ethereal layer and interfacial debris discarded, and the filtered aqueous solution adjusted to pH 8 with 50% NH_4OH. Crude VII separated as a granular beige solid (1.36 g, 92%). Further purification of VII in the form of its hydrochloride was achieved by dissolving VII in a minimum of 1N HCℓ and placing the solution on a 50 mL column of Dowex 50W-X4, previously washed with 3N HCℓ followed by H_2O until neutral. The column was then washed with H_2O, 100 mL of 0.5N HCℓ and 200 mL of 1N HCℓ. The hydrochloride of VII was eluted from the column with twelve 100 mL portions of 3N HCℓ and recovered by lyophilization as an analytically pure light sensitive, hygroscopic, off-white solid. Mass spectrometry and NMR confirmed its identity as VII·HCℓ.

Anal. Calcd for $C_8H_{11}C\ell INO_3$: C, 28.99; H, 3.34; N, 4.22.

Found: C, 28.70; H, 3.85; N, 4.14.

NMR(D_2O): δ 3.18 (m, 2H, $-CH_2-$) 4.85 (m, partially obscured by OH peak, -CH-), 6.89 (d, 1H, benzene C_2-H, J = 1.5Hz), 7.31 (d, 1H, benzene C_6-H, J = 1.5Hz).

Mass spectrum (CH_4): 296 ((M-HCℓ) + 1, 4.7%), 257 (3%), 202 (5.3%), 157 (90%), 129 (100%).

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8. It should be noted that the direction of numbering of ring carbon atoms is reversed from that used for the trivial names, 5-iodovanilin and 5-iodonorepinephrine.

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