Hydroxycarbamonitriles from the Reaction of Amino Alcohols with Cyanogen Bromide[1]

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The reaction of cyanogen bromide with *trans*-2-amino-1,2,3,4-tetrahydro-1-naphthol or a *trans*-2-amino-*p*-menthan-1-ol affords crystalline 1-hydroxy-2-carbamonitriles which have been cyclized to the *trans*-2-amino-2-oxazolines. The reaction of *cis*-3-amino-2,2,4,4-tetramethyl-1-cyclobutanol with cyanogen bromide gives a hydroxycarbamonitrile which is not cyclized by either acid or base.

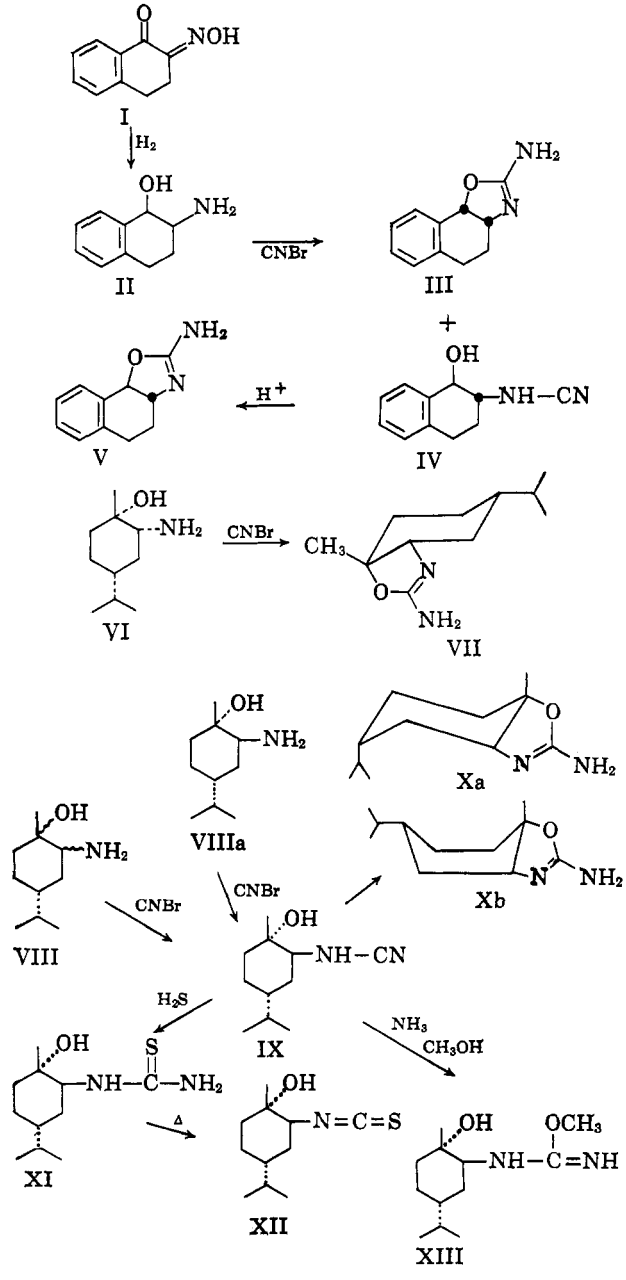
The preparation of 2-amino-2-oxazolines by reaction of 1,2-amino alcohols with cyanogen bromide has been previously described.[2] As has been reported,[2a,3,4] the intermediate hydroxycarbamonitriles (cyanamides) were found to cyclize spontaneously in every case and were not isolable. Meschino and Bond[5] have recently described the preparation of several 5-substituted 2-amino-5,6-dihydro-4H-1,3-oxazines by cyclization of 1,3-amino alcohols with cyanogen bromide. In contrast to the 1,2-amino alcohols, the intermediate hydroxy cyanamides could be isolated in most cases, and one such intermediate was characterized.

A further study of the reaction of several 1,2- and 1,3-amino alcohols with cyanogen bromide has led to the isolation and characterization of additional uncyclized hydroxy cyanamides from both series of compounds. In all cases these were derived from amino alcohols which were difficult to cyclize for steric reasons.

Low pressure hydrogenation of 3,4-dihydro-2-oximino-1-naphthalenone (I) gave a mixture of *cis*- and *trans*-1,2-amino alcohols II which was treated directly with cyanogen bromide.[2b] The reaction mixture was separated into a basic and a neutral fraction. From the basic fraction there was isolated a crystalline amino oxazoline. Since this compound was obtained by spontaneous cyclization of the intermediate hydroxycarbamonitrile, the *cis* structure III is assigned.[6] The neutral fraction afforded a crystalline hydroxy cyanamide to which the *trans* structure IV is assigned.[6] On treatment with hydrogen chloride in methylene chloride, IV provided the *trans*-2-amino-2-oxazoline (V). Although the yields of III and IV were low, they were found to be reproducible. (See Chart I.)

Several terpene-1,2-amino alcohols were found to react with cyanogen bromide in a manner similar to the tetrahydronaphthalene-1,2-amino alcohol (II). The configuration of the *cis*-2-amino-*p*-menthan-1-ol (VI) has been previously established by its preparation from a *trans*-*p*-menthane-1,2-diol of known configuration.[7] On reaction with cyanogen bromide, VI gave the *cis*-2-aminohexahydrobenzoxazole (VII) in 47% yield. The ease of formation of the conformationally favorable aminooxazoline VII and the absence of any uncyclized hydroxy cyanamide in the reaction product is further evidence for the *cis* configuration of the hydroxyl and amino groupings in VI.

CHART I



(1) Florida Agricultural Experiment Stations Journal Series No. 1841.

(2) (a) R. R. Wittekind, J. D. Rosenau, and G. I. Poos, *J. Org. Chem.*, **26**, 444 (1961); (b) G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszkowski, N. M. Kelley, and J. McGowin, *J. Med. Chem.*, **6**, 266 (1963).

(3) G. Fodor and K. Koczka, *J. Chem. Soc.*, 850 (1952).

(4) E. Fromm and R. Kapeller-Alder, *Ann.*, **467**, 240 (1928).

(5) J. A. Meschino and C. H. Bond, *J. Org. Chem.*, **28**, 3129 (1963).

(6) These structural assignments have been confirmed by n.m.r. studies of the isomeric aminooxazolines III and V. These data will be published separately by Dr. H. R. Almond, Jr., of McNeil Laboratories.

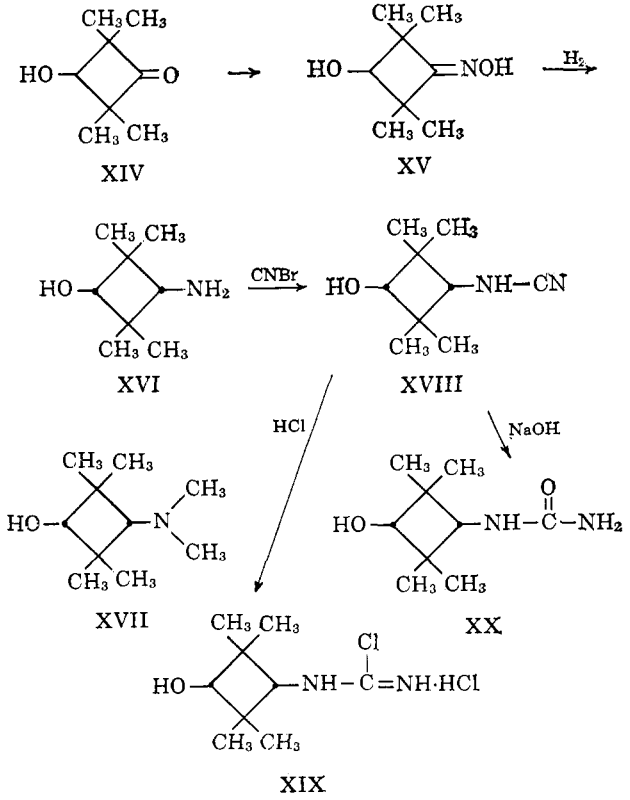
(7) W. F. Newhall, *J. Org. Chem.*, **24**, 1673 (1959).

The mixed *trans*-amino alcohols VIII, prepared by the cleavage of *p*-menthane 1,2-epoxide with ammonia,[7] in contrast to VI gave a neutral reaction product with cyanogen bromide from which a single, crystalline hydroxy cyanamide IX was isolated in 59% yield. The remainder of the reaction product was a neutral, amorphous glass which showed strong C≡N absorption at 4.5 μ in the infrared. However, the *trans*-hydroxy cyanamide isomeric with IX could not be isolated.

The configuration of IX was established by its preparation in 80% yield from the reaction of the *trans*-2-amino-*p*-menthan-1-ol (VIIIa) with cyanogen bromide. The configuration of VIIIa has been previously established by its preparation from *trans*-*p*-menthane-1,2-diol of known stereochemistry.[7]

The failure of the hydroxy cyanamide IX to cyclize spontaneously is easily understood by an examination of possible chair and boat conformers Xa and Xb of the ring closed product. Both Xa and Xb have a number of unfavorable interactions. Despite this, hydroxy cyanamide IX was found to cyclize in 28% yield by heating in methanol containing clay boiling stones (Boileezers). Apparently this cyclization was due to mild alkaline catalysis for it could be prevented by pretreatment of the boiling stones with dilute hydrochloric acid. Other weak bases such as sodium acetate gave much lower yields of X than those obtained using Boileezers. The *trans*-hydroxy cyanamide IX did not cyclize under other basic reaction conditions.

Additions across the nitrile triple bond of IX occurred readily. In ethanolic triethanolamine, hydrogen sulfide added to give the crystalline hydroxythiourea XI in good yield (70%). On heating under vacuum, XI lost ammonia and was converted smoothly to the liquid isothiocyanate XII. Treatment of IX with methanolic ammonia resulted in the addition of methanol to afford the methylpseudourea XIII.



The reaction of *cis*-3-amino-2,2,4,4-tetramethyl-1-cyclobutanol (XVI) with cyanogen bromide was also studied. Amino alcohol XVI was prepared by catalytic hydrogenation of oxime XV which was prepared from ketol XIV[8] by partial catalytic hydrogenation of dimethylketene dimer. Evidence for the assignment of *cis* stereochemistry to amino alcohol XVI was obtained by conversion to the N,N-dimethyl derivative XVII (m.p. 129)°. Compound XVII is reported to melt at 129–130° while the corresponding *trans* isomer melts at 70–72°.[9]

The sole product from the reaction of aminocyclobutanol XVI and cyanogen bromide was the hydroxy cyanamide XVIII. On treatment with hydrogen chloride in tetrahydrofuran, XVIII gave the chloroformamidine hydrochloride XIX by addition to the nitrile bond. With strong aqueous alkali, XVIII was hydrolyzed to the cyclobutylurea XX in good yield. Thus, as would be expected, this 1,3-cyclobutyl system is resistant to cyclization for steric reasons.

Experimental

***cis*-2-Amino-3a,4,5,9b-tetrahydronaphth[2,1]oxazole (III) and *trans*-1-Hydroxy-1,2,3,4-tetrahydro-2-naphthalenecarbamonitrile (IV).**—A 10.0-g. sample (0.057 mole) of 3,4-dihydro-2-oximino-1-naphthalenone (I) was hydrogenated over 0.8 g. of platinum oxide in 200 ml. of absolute methanol on a Parr shaker. The theoretical amount of hydrogen was consumed in 10 min., and the reaction was stopped after an additional 10 min.

Under a stream of nitrogen, the reduction mixture was poured into a solution of 14 g. (0.171 mole) of sodium acetate in 50 ml. of water. After cooling to 0°, the mixture was treated with a solution of 6.6 g. (0.0627 mole) of cyanogen bromide in 50 ml. of methanol. The reaction mixture was stirred at 0° for 2.5 hr., made basic with aqueous ammonia, filtered, and concentrated *in vacuo* to remove the methanol. It then was diluted with water, acidified with dilute hydrochloric acid, and extracted three times with ether. From the ether extracts there was obtained 1.1 g. of neutral product. This material was recrystallized from acetone–benzene (Norit–Darco) to give 0.92 g. (8.6% from I) of IV, m.p. 111–114°; λ_{max}^{KBr} 2.98, 3.47, 4.54, 5.8 (w), 6.26 (w), 6.70, 6.88, and 6.96 μ.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.22; H, 6.53; N, 15.09, 15.23.

The acidic solution was made basic with sodium hydroxide and extracted with methylene chloride. The extracts afforded 3.5 g. of basic material. After two recrystallizations from benzene (Norit–Darco), there was obtained 1.23 g. (11.5%) of III, m.p. 150.5–153.5°; λ_{max}^{KBr} 2.93, 3.30, 3.42, 5.93, 6.25, 6.69, 6.88, 6.93, and 7.05 μ.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.20; H, 6.62; N, 15.16.

A sample of III was converted to its fumarate salt, m.p. 159–169° after recrystallization from ethanol; λ_{max}^{KBr} 3.45, 5.84, 6.60, 6.88 (w), 6.98 (w), and 7.38 μ.

Anal. Calcd. for $(C_{11}H_{12}N_2O)_3 \cdot (C_4H_4O_4)_2$: N, 10.52. Found: N, 10.59.

***trans*-2-Amino-3a,4,5,9b-tetrahydronaphth[2,1]oxazole (V) from *trans*-1-Hydroxy-1,2,3,4-tetrahydro-2-naphthalenecarbamonitrile (IV).**—A 0.175-g. sample of IV was dissolved in methylene chloride and treated with ethereal hydrogen chloride, affording 0.2 g. of amine salt; λ_{max}^{Nujol} 3.35, 3.45, 5.85, 6.25, 6.45, 6.7, 6.85, and 7.28 μ.

The salt was dissolved in 5% sodium hydroxide and extracted into methylene chloride. The extracts were dried and concentrated, and the base was twice recrystallized from methylene chloride–ether, giving 0.035 g. of V, m.p. 136–137.5°, m.p. 133.5–147° when mixture melted with III; λ_{max}^{KBr} 2.89, 3.2, 3.33, 3.41, 3.46, 5.86, 5.93, 6.08, 6.23, 6.67, 6.77, 6.85, and 7.03 μ. The infrared spectra of III and IV were clearly different.

(8) R. H. Hasek, E. V. Elam, J. C. Martin, and R. G. Nations, *J. Org. Chem.*, **26**, 700 (1961).

(9) R. H. Hasek and J. C. Martin, *ibid.*, **28**, 1468 (1963).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.67; H, 6.48; N, 14.95.

***cis*-2-Amino-5-isopropyl-7a-methyl-3a,4,5,6,7,7a-hexahydrobenzoxazole (VII).**—A suspension of 2.8 g. (0.070 mole) of crushed sodium hydroxide pellets in 90 ml. of dry benzene containing 11.8 g. (0.069 mole) of dissolved *cis*-2-amino-*p*-menthan-1-ol (VI) was stirred and cooled at 5° during the dropwise addition of a solution of 7.31 g. (0.069 mole) of cyanogen bromide in 40 ml. of dry benzene. The cooling bath then was removed and the mixture was stirred at room temperature for 16 hr. The precipitated salts were collected on a filter and the filter cake was washed twice with benzene and once with ether. Concentration of the filtrate under vacuum gave a viscous residue which rapidly crystallized (prisms). These crystals were collected on a filter and washed with cold petroleum ether (b.p. 30–60°). This procedure gave 6.34 g. (47%) of *cis*-2-amino-5-isopropyl-7a-methyl-3a,4,5,6,7,7a-hexahydrobenzoxazole (VII), m.p. 93–96.5°, which was soluble in most common organic solvents and dilute aqueous acids but was insoluble in water. Several recrystallizations from petroleum ether afforded a sample melting at 96.8–97.8°; $[\alpha]^{25}D$ +42.3° (*c* 10.0, acetone); λ_{max}^{KBr} 2.94, 3.39, 3.49, 5.88, 5.98, 6.21, 6.80, 6.88, 7.08, and 9.67 μ.

Anal. Calcd. for $C_{11}H_{20}N_2O$: C, 67.30; H, 10.27; N, 14.27. Found: C, 67.44; H, 9.76; N, 14.42.

The *trans*-1-Hydroxy-*p*-menthane-2-carbamonitrile (IX) from the Mixed *trans* Isomers of VIII.—A solution of 14 g. (0.082 mole) of mixed *trans*-2-amino-*p*-menthan-1-ols (VIII) and 21.8 g. (0.160 mole) of sodium acetate trihydrate in 100 ml. of methanol was stirred at 0–5° during the dropwise addition of a solution of 9.50 g. (0.089 mole) of cyanogen bromide in 50 ml. of methanol (20 min.). The clear solution then was stirred and allowed to warm to room temperature (55 min.). Twelve milliliters of ammonium hydroxide was added and most of the methanol was removed under vacuum. Four hundred milliliters of water was added and the product crystallized. The crystals were collected on a filter, washed with water, and recrystallized from ethanol–water solution. This procedure gave 9.5 g. (59%) of *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX), m.p. 154–156.6°, which was very sparingly soluble in water and soluble in most common organic solvents. A sample purified by repeated recrystallization from aqueous ethanol melted at 158.2–158.4°; $[\alpha]^{25}D$ +81.4° (*c* 10.0, ethanol); λ_{max}^{KBr} 2.98, 3.14, 3.36, 3.46, 4.48, 6.63, 6.79, 6.86, 8.28, and 9.79 μ.

Anal. Calcd. for $C_{11}H_{20}N_2O$: C, 67.30; H, 10.27; N, 14.27. Found: C, 67.56; H, 10.58; N, 13.96.

***trans*-1-Hydroxy-*p*-menthane-2-carbamonitrile (IX) from *trans*-2-Amino-*p*-menthan-1-ol[7] (VIIIa).**—A solution of 1.43 g. (0.0083 mole) of the pure *trans*-2-amino-*p*-menthan-1-ol (VIIIa) and 2.18 g. (0.016 mole) of sodium acetate trihydrate in 10 ml. of methanol was stirred at 0–5° during the dropwise addition of a solution of 0.95 g. (0.0090 mole) of cyanogen bromide in 5 ml. of methanol. The same reaction conditions described above were used and the product was isolated in the same manner. This procedure afforded 1.32 g. (80%) of the *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX), m.p. 154–155.5° which was identical in all respects, including infrared absorption, with a sample of IX prepared from VIII.

***trans*-2-Amino-5-isopropyl-7a-methyl-3a,4,5,6,7,7a-hexahydrobenzoxazole (X).**—One gram of *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX) was dissolved in 25 ml. of methanol and the solution was refluxed for 2 hr. with 5 g. of Boileezers.[10] The mixture was filtered and the filtrate was concentrated to dryness under vacuum. The basic, amorphous residue was converted to a picrate salt by treatment with excess picric acid in benzene–methanol solution. This procedure gave 0.62 g. (28%) of the crude picrate of X as yellow prisms, m.p. 146–152°. Two recrystallizations from benzene–methanol solution afforded 0.49 g., m.p. 154–155°.

Anal. Calcd. for $C_{17}H_{23}N_5O_8$: C, 48.00; H, 5.45; N, 16.46. Found: C, 47.75; H, 5.76; N, 15.86.

The free base X, regenerated from the picrate by treatment with dilute, aqueous sodium hydroxide followed by ether extraction, was an amorphous glass. This material was sublimed under vacuum to give a colorless glass which was a strong base soluble in ether and most organic solvents; $[\alpha]^{25}D$ +74.9° (*c* 8.0, acetone); $\lambda_{max}^{CCl_4}$ 2.89, 2.96, 3.37, 3.46, 5.88, 6.03, 6.28, 6.55, 6.82, 6.93, 7.29, 7.52, 9.14, and 9.70 μ.

1-(*trans*-1-Hydroxy-*p*-menth-2-yl)-2-thiourea (XI).—Twenty-four grams of *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX) was dissolved in a solution of 81 ml. of triethanolamine in 400 ml. of absolute ethanol. Hydrogen sulfide was bubbled into the solution for 2 hr. with stirring at a temperature of 50°. The solution was cooled to room temperature, again saturated with hydrogen sulfide, stoppered, and left at room temperature for 4 days. It was then concentrated under vacuum. The residual oil was dissolved in ether and the ether phase was washed three times with 6 *N* hydrochloric acid and finally with water until neutral. Removal of the ether under vacuum gave a colorless, solid residue which was dissolved in ethanol–water. The hot solution was treated with Darco-G60, filtered, and concentrated. When cooled, colorless needles of 1-(*trans*-1-hydroxy-*p*-menth-2-yl)-2-thiourea (XI) separated from the solution. This procedure afforded 21.5 g. (70%) of XI, m.p. 90–94°. A small sample, purified by repeated crystallizations from methanol–water solution, melted at 93–94.5° with bubbling and apparent decomposition; $[\alpha]^{25}D$ +70.9° (*c* 10, acetone); λ_{max}^{KBr} 3.02, 3.14, 3.38, 3.47, 6.09, 6.17, 6.43, 6.83, 7.03, 7.31, and 9.04 μ.

Anal. Calcd. for $C_{11}H_{22}N_2OS$: C, 57.34; H, 9.63; N, 12.16; S, 13.92. Found: C, 56.76; H, 9.76; N, 11.60; S, 13.69.

1-Hydroxy-*p*-menthane-2-isothiocyanate (XII).—Five grams of 1-(*trans*-1-hydroxy-*p*-menth-2-yl)-2-thiourea (XI) was vacuum distilled at 160–170° (0.5 mm.) over a very short path in order to avoid excessive heating. Two 25-ml. round-bottomed flasks connected by a short U tube were used. Decomposition proceeded smoothly with the evolution of ammonia and the isothiocyanate XII distilled as a colorless, slightly viscous liquid (3 g., 65%). After two redistillations, 1 g. of isothiocyanate was obtained which distilled at a pot temperature of 110–115° (0.25 mm.); $n^{25}D$ 1.5265; λ_{max}^{KBr} 2.86, 3.36, 3.45, 4.62, 4.75, 6.81, 7.28, and 8.30 μ.

Anal. Calcd. for $C_{11}H_{19}NOS$: C, 61.92; H, 8.98; N, 6.57; S, 15.03. Found: C, 62.38; H, 9.06; N, 6.44; S, 14.87.

2-Methyl-3-(*trans*-1-hydroxy-*p*-menth-2-yl)pseudourea (XIII).—Five grams of *trans*-1-hydroxy-*p*-menthane-2-carbamonitrile (IX) was dissolved in 100 ml. of 8% ammoniacal methanol. The resulting solution was stirred and heated at 110–120° in a bench-scale autoclave for 2 hr. and finally concentrated to dryness under vacuum. The colorless, oily product was dissolved in methanol–water and sufficient solid picric acid was added to make the solution strongly acidic. This procedure gave 5.7 g. (49%) of XIII picrate, m.p. 109–112°. On recrystallization from benzene–methanol solution, the picrate lost solvent of crystallization and crystallized as yellow needles, m.p. 133–135°. This anhydrous picrate showed a tendency to darken on exposure to light; λ_{max}^{KBr} 2.83, 2.93, 3.08, 3.24, 3.38, 5.91, 6.07, 6.36, 7.29, 7.45, and 8.92 μ.

Anal. Calcd. for $C_{18}H_{27}N_5O_9$: C, 47.26; H, 5.95; N, 15.31; CH_3O–, 6.77. Found: C, 47.37; H, 5.87; N, 15.15; CH_3O–, 7.57.

3-Hydroxy-2,2,4,4-tetramethylcyclobutanone (XIV).—A mixture of 20 g. (0.14 mole) of tetramethylcyclobutane-1,3-dione, 2 ml. of triethylamine, and 1.5 teaspoonfuls of nickel sponge catalyst[11] in 250 ml. of absolute ethyl alcohol was hydrogenated in a Parr shaker. The theoretical amount of hydrogen was taken up in 70 min. The mixture was filtered and the catalyst was washed with 50 ml. of ethyl alcohol. The combined solution was evaporated to afford 20 g. of crude product. After one recrystallization from water, 19 g. (95%) of 3-hydroxy-2,2,4-4-tetramethylcyclobutanone (XIV), m.p. 112–114° (lit.[8] m.p. 114°), was obtained; λ_{max}^{KBr} 2.97, 3.41, 3.52, 5.75, 9.05, 9.69, 9.84, and 12.02 μ.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.29; H, 9.90.

3-Hydroxy-2,2,4,4-tetramethylcyclobutanone Oxime (XV).—To a solution of 15.3 g. (0.125 mole) of the ketol (XIV) in 135 ml. of 50% ethyl alcohol was added 9.2 g. (0.13 mole) of hydroxylamine hydrochloride and a solution of 10.7 g. (0.13 mole) of sodium acetate in 35 ml. of water. The solution was heated on a steam bath for 5 min. and then stirred at room temperature for 12 hr. Water (100 ml.) was added and the mixture was stirred at room temperature overnight. The product was separated by filtration and recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°) to give 13.5 g. (68%) of the oxime XV, m.p. 147–152°; λ_{max}^{KBr} 3.11 and 5.94 μ.

(10) Supplied by Fisher Scientific Co.

(11) Supplied by Davison Chemical Co.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.98; H, 9.61; N, 8.73.

***cis*-3-Amino-2,2,4,4-tetramethyl-1-cyclobutanol (XVI).**—A mixture of 10 g. (0.064 mole) of the oxime XV and 2 teaspoonfuls of nickel catalyst[11] in 100 ml. of absolute ethanol was hydrogenated on a Parr shaker. The reduction was rapid and within 20 min. the theoretical amount of hydrogen was taken up. The mixture was filtered and the solvent was distilled under diminished pressure to obtain 10 g. (theoretical yield) of crude XVI; $\lambda_{max}^{CHCl_3}$ 3.07, 6.24, 6.86, 8.93, and 9.5 μ.

Five grams (0.036 mole) of the free base XVI in anhydrous ether was converted to the corresponding amine hydrochloride by treating the solution with hydrogen chloride. After recrystallization from ethanol–ether, 4.5 g. (over-all 80%) of *cis*-amino alcohol XVI hydrochloride, m.p. 243–245° dec., was obtained; λ_{max}^{KBr} 3.03, 4.77, 6.14, 6.57, 7.45, 8.95, 9.58, and 9.95 μ.

Anal. Calcd. for $C_8H_{17}NO \cdot HCl$: C, 53.50; H, 10.11; N, 7.80. Found: C, 53.70; H, 10.25; N, 7.55.

***cis*-3-Dimethylamino-2,2,4,4-tetramethyl-1-cyclobutanol (XVII).**—Thirty-seven grams (0.7 mole) of cold 88% formic acid was added to 20 g. (0.14 mole) of the *cis*-aminocyclobutanol XVI, and to the resulting clear solution was added 34 g. (0.42 mole) of 37% formaldehyde solution. The mixture was placed in an oil bath which had been heated to 100°. A vigorous evolution of carbon dioxide began after 3–5 min., at which time the reaction mixture was removed from the bath until the gas evolution notably subsided; then it was returned to the bath and heated at 100° for 18 hr. After the mixture was cooled, hydrochloric acid (30 ml. of concentrated hydrochloric acid in 70 ml. of distilled water) was added and the acidic solution was distilled under diminished pressure to remove the solvent. The resulting sirupy residue was dissolved in 80 ml. of water, made basic by the addition of 100 ml. of 30% sodium hydroxide, and extracted with three 150-ml. portions of ether and three 150-ml. portions of methylene chloride.

The combined solution was dried over anhydrous magnesium sulfate and the solvent was distilled under diminished pressure, giving 18 g. (75%) of *cis*-3-dimethylamino-2,2,4,4-tetramethyl-1-cyclobutanol (XVII), m.p. 115–118°. Recrystallization from hexane gave a sample melting at 129° (lit.[9] m.p. 129–130°); λ_{max}^{KBr} 3.16, 3.58, and 3.65 μ.

A 6.6-g. sample (0.038 mole) of the free base in anhydrous ether was converted to the corresponding amine hydrochloride by treating the solution with hydrogen chloride. After one recrystallization from ethanol–ether, 6.3 g. (over-all 64%) of *cis*-3-dimethylamino-2,2,4,4-tetramethyl-1-cyclobutanol hydrochloride, m.p. 292–293° dec., was obtained; λ_{max}^{KBr} 3.12, 3.50, 3.84, 6.76, 6.81, 7.43, 7.60, 8.15, 8.34, 8.75, and 8.94 μ.

Anal. Calcd. for $C_{10}H_{21}NO \cdot HCl$: C, 57.56; H, 10.20; N, 6.74. Found: C, 57.37; H, 10.30; N, 6.66.

***cis*-3-Hydroxy-2,2,4,4-tetramethyl-1-cyclobutylcarbamonitrile (XVIII).**—To a solution of 5 g. (0.035 mole) of the 3-aminocyclobutanol XVI and 3.1 g. (0.037 mole) of sodium acetate in 50 ml. of 95% methanol was added, with cooling a solution of 3.9 g. (0.037 mole) of cyanogen bromide in 25 ml. of methanol. The resulting solution was allowed to stand at room temperature for 90 min. and the solvent was distilled under diminished pressure. A 75-ml. portion of water was added to the residue. The resulting white solid was filtered and recrystallized from benzene to give 3 g. (51%) of the hydroxycyclobutylcarbamonitrile XVIII, m.p. 164–166°; λ_{max}^{KBr} 2.96, 4.48, 8.45, and 9.07 μ.

Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.25, H, 9.59; N, 16.65. Found: C, 64.46; H, 9.75; N, 16.42.

Chloro-N-(*cis*-3-hydroxy-2,2,4,4-tetramethyl-1-cyclobutyl)-formamidine Hydrochloride (XIX).—A solution of 7.8 g. (0.046 mole) of *cis*-3-hydroxy-2,2,4,4 tetramethyl-1-cyclobutylcarbamonitrile (XVIII) in 80 ml. of anhydrous tetrahydrofuran was cooled in an ice bath. An excess of hydrogen chloride was dissolved in the solution and the resulting reaction mixture was allowed to stand at room temperature. The precipitated product was filtered and dried to give 7.5 g. (67%) of chloroformamidine hydrochloride (XIX), m.p. 162–164°; λ_{max}^{KBr} 2.93, 6.01, 6.19, 9.07, and 9.53 μ.

Anal. Calcd. for $C_9H_{17}ClN_2O \cdot HCl$: N, 11.61. Found: N, 11.58.

(*cis*-3-Hydroxy-2,2,4,4-tetramethyl-1-cyclobutyl)urea (XX).—A solution of 1 g. (0.006 mole) of *cis*-3-hydroxy-2,2,4,4-tetramethylcyclobutylcarbamonitrile (XVIII) in 80 ml. of 60% sodium hydroxide solution was allowed to stand at room temperature for 15 hr. The resulting white solid product was filtered and recrystallized from benzene–ethanol to give 0.7 g. (63%) of the hydroxycyclobutylurea XX, m.p. 183–184°; λ_{max}^{KBr} 2.95, 3.07, 6.02, 6.18, and 9.25 μ.

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 58.31; H, 9.91; N, 14.76.

Model Reactions for the Biosynthesis of Thyroxine. VI. Structural Requirements of Analogs of Diiodotyrosine in the Reaction with 4-Hydroxy-3,5-diiodophenylpyruvic Acid to Form Analogs of Thyroxine[1,2]

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To contribute to the understanding of the mechanism by which thyroxine is formed in good yield from 4-hydroxy-3,5-diiodophenylpyruvic acid (I) and 3,5-diiodotyrosine in the presence of oxygen, keto acid I was permitted to react in a similar fashion with a series of analogs of diiodotyrosine. The dependence of the formation of the corresponding analogs of thyroxine on various structural features of the analogs of diiodotyrosine used has been investigated.

The biosynthetic mechanism by which thyroxine is formed from diiodotyrosine has not yet been elucidated. A few years ago, Meltzer and Stanaback[4] reported that 4-hydroxy-3,5-diiodophenylpyruvic acid (I) couples with 3,5-diiodotyrosine [IIa, X = I; R = $CH_2CH(NH_2)COOH$] in the presence of oxygen at a neutral or slightly alkaline pH to form thyroxine rapidly and in good yield. Shiba and Cahnmann[5] extended the investigation to the preparation of radioactive products. They proved that the phenolic ring of the thyroxine [IIIa, X = I; R = $CH_2CH(NH_2)COOH$] formed is derived from 4-hydroxy-3,5-diiodophenylpyruvic acid (I), and the nonphenolic ring and its alanine side chain from 3,5-diiodotyrosine (IIa). More recently the same authors found that rattlesnake venom, in the presence of oxygen and of catalase, can convert diiodotyrosine

(1) Previous paper in this series, T. Shiba and H. J. Cahnmann, *J. Org. Chem.*, **29**, 1652 (1964); for first paper in this series see ref. 8.

(2) This paper has been presented at the 16th Annual Meeting of the Chemical Society of Japan, April, 1963, Tokyo, Japan.

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(4) R. I. Meltzer and R. J. Stanaback, *J. Org. Chem.*, **26**, 1977 (1961).

(5) T. Shiba and H. J. Cahnmann, *ibid.*, **27**, 1773 (1962).