1-nitronaphthalene (II), m.p. 90.2–91.2°, which was prepared in turn (70%) from 5-chloromethyl-1-nitronaphthalene (I)[3] by an acetolysis procedure described by Short and Wang.[3]

A 4.90 g. (0.0200 mole) portion of II was suspended in 45 ml. of 0.44*N* alcoholic potassium hydroxide, and the mixture refluxed for 3 hr. By concentrating the resultant solution *in vacuo*, and adding water to it, a brown precipitate was formed. By collecting this precipitate, washing it with water, then with *n*-hexane, and desiccating it, 4.02 g. (99%) of III, m.p. 128–129°, was obtained. The product was recrystallized from hot 1:1 chloroform/cyclohexane to pale yellow needles, m.p. 130.4–131.2°. (Compare with m.p. 128–129° reported for III by Short and Wang[3] as prepared by hydrolysis of I with aqueous sodium carbonate.)

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.01; H, 4.46; N, 6.89. Found: C, 65.27; H, 4.37; N, 6.79, 6.83.

5-Hydroxymethyl-1-naphthylamine (IV). A 10.16 g. (0.0500 mole) quantity of III, m.p. 128–129°, was dissolved in 200 ml. of warm absolute ethanol, and the solution poured into a 375 ml. Parr hydrogenation pressure bottle, and allowed to cool. Water-wet, active Raney nickel catalyst (2.9 g.) was added to the bottle, which was connected to a Parr low pressure hydrogenation apparatus. The system was swept with hydrogen and reduced with hydrogen at an initial pressure of three atmospheres, at 25° with mechanical shaking, for 4 hr. (to constant pressure value of gas reservoir). Then the solution was exposed to the system for another hour at 75° (during which time no further drop in hydrogen pressure occurred). After filtering the catalyst from the hot solution (quickly flushing the pyrophoric residue into the sink), the ethanol solution was evaporated *in vacuo*. In this way, 8.13 g. (93.6%) of fairly pure IV was obtained as a brown solid m.p. 106.4–107.4°. On recrystallizing the product from hot 7:1 toluene/ethanol solution, orange-brown crystals, m.p. 107.2–108.4°, with an equivalent weight of amine of 175 (on basis of titration with perchloric acid in acetic acid with methyl violet indicator), as compared with a theoretical equivalent weight of 173 for $C_{11}H_{11}NO$, were obtained.

Bis(5-hydroxymethyl-1-naphthyl) disulfide (VI). (A) Formation of crude 5-hydroxymethyl-1-thionaphthol (V). A 3.98 g. (0.0230 mole) quantity of IV was mixed with 5.76 ml. of concentrated hydrochloric acid and 15 ml. of water. To this yellow-green slurry, cooled to −5°, was added an ice-chilled solution of 1.59 g. of sodium nitrite in 5 ml. of water, gradually with stirring, along with some ice. This brown diazonium salt suspension was added, dropwise, with stirring to a solution of 5.60 g. (0.0350 mole) of potassium ethyl xanthate in 10 ml. of water, maintaining the latter system at 50°, and the former at 0°. After mixing, the system was maintained at 50° for an additional hour, with continued stirring, and allowed to cool. After acidification with 1:1 concentrated sulfuric acid/water in the hood, the system was extracted with ether and the solvent removed. The resultant 5.30 g. of crude 5-hydroxymethyl-1-naphthyl ethyl xanthate was hydrolyzed by treating with a solution containing 3.46 g. potassium hydroxide, 1 ml. of water, and 5 ml. of ethanol at reflux for 1 hr. After removal of ethanol *in vacuo*, the residue was extracted with 100 ml. of water, and the aqueous extract acidified with 6*N* sulfuric acid. The brown precipitate which formed was collected, washed with water, then with hexane, and air dried. This crude 2.68 g. of thiol (V), m.p. 73–76°, was obtained in 61% yield of product of 58% thiol activity (on the basis of potentiometric titration of an ammoniacal solution of V in isopropanol with standardized silver nitrate).

(B) Disulfide formation. A 1.96 g. quantity of V (containing 0.00600 mole of active V) was dissolved in 30 ml. of ethanol, and treated with a solution of 0.76 g. (0.0060 gram atoms) of iodine in aqueous potassium iodide solution. By collecting, washing, and drying the resultant yellow precipitate, 1.34 g. of solid, m.p. 178–185°, was obtained. On recrystallizing this product from 60 ml. of 4:2:1 toluene/ethanol/nitrobenzene solution, 0.56 g. of VI, m.p. 193–194°, was isolated. This was recrystallized from 5:1 ethanol/nitrobenzene to tan crystals, m.p. 196–197°. The latter substance gave a negative test for mercaptan with silver nitrate reagent, but did form the silver mercaptide after being reduced with aqueous sodium sulfite (the latter test confirms presence of the disulfide function).

Anal. Calcd. for $(C_{11}H_9OS)_2$: C, 69.85; H, 4.80; S, 16.95. Found: C, 69.18, 69.30; H, 4.57, 4.68; S, 17.38, 17.46.

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Resolution of DL-β-Hydroxybutyric Acid

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Received May 28, 1959

The resolution of racemic β-hydroxybutyric acid, described in 1902 by McKenzie[2] and repeated by Levene and Haller,[3] depends primarily on inoculation of an aqueous solution of the quinine salts with a crystalline sample of the salt of the L acid obtained from diabetic urine.

In the procedure here described advantage is taken of the hitherto unrecorded great difference in the solubility in acetone of the two quinine salts, the D variety of which requires nearly ten times as much of the solvent as the L isomer for solution. The relationships are illustrated in Table I.

TABLE I

APPROXIMATE PERCENTAGE CONCENTRATION OF SATURATED SOLUTIONS OF THE QUININE SALTS OF D- AND L-β-HYDROXYBUTYRIC ACIDS IN ACETONE AND IN WATER AT VARIOUS TEMPERATURES

Acetone		Water	
D	L	D	L
0.49/1°	4.4/1°	3.5/0°	2.6/0°
1.33/21°	13.2/25°	4.0/25°	5.8/25°
		10/60°	10/36°

EXPERIMENTAL

To a hot solution of 200 meq. of DL-β-hydroxybutyric acid (91.3% by titration) in 500 ml. of acetone, 65 g. (200 mmoles) of anhydrous quinine base was gradually added. When solution was complete the mixture was chilled at 0–1° for 24 hr.; the crystalline salt was collected with suction, washed with 50 ml. of ice cold acetone, and then digested with 300 ml. of boiling acetone for 30 min. The suspension was cooled, held at 0–1° overnight, and filtered with suction; the crystals were washed with 30 ml. of cold acetone, digested as before with 150 ml. of boiling acetone, and dried in air. The yield was 36 g. (81 mmoles, calculated as monohydrate) of quinine D-β-hydroxybutyrate.

(1) Present address: Department of Biochemistry, Yale University, New Haven, Conn.

(2) A. McKenzie, *J. Chem. Soc.*, **81**, 1402 (1902).

(3) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **65**, 49 (1925).

The acetone in the combined filtrates and washings was removed as completely as possible by distillation from a steam bath; the sirupy residue was dissolved in 100 ml. of water, the solution was gently warmed until the odor of acetone was no longer perceptible, and was then chilled at 0–1° for 2 days. The needle crystals of quinine L-β-hydroxybutyrate were collected with suction and washed with 10 ml. of ice water in small portions, and the adhering solution was largely displaced by washing with ether. The product was then recrystallized from 80 ml. of water as before, washed with 10 ml. of ice water and finally with ether.[4] After being dried in air, the crystals, which weighed 31.3 g., were dried *in vacuo* to constant weight, 26.1 g. These values correspond to 62 mmoles of the hydrated (4.5 H_2O) and anhydrous salts, respectively.

The free acids were liberated by the gradual addition of 45-ml. quantities of 45% H_2SO_4 to suspensions of the above products in 100 ml. of water. During this operation, quinine sulfate crystallized at first but later dissolved with the formation of the more soluble acid sulfate. The optically active β-hydroxybutyric acids were extracted in a continuous apparatus by a rapid current of ether during 8 hr. and after the removal of solvent the residues were dissolved in water. The solutions were cleared with Norit and aliquots taken for titration and measurement of rotation. The 81 mmoles of D salt yielded 75 mmoles of D acid, $[\alpha]_D^{25} = +23.9°$. The 62 mmoles of L salt yielded 58 mmoles of L acid, $[\alpha]_D^{25} = -24.5°$.

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(4) The yields of both salts could no doubt be materially increased by evaporation of the aqueous filtrates to dryness and repetition of the crystallizations from acetone and water.

α-Alkyloximino Aldehydes[1]

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Received May 28, 1959

Certain α-oximino acids, R—C(=NOH)—COOH, and α-alkyloximino acids, R—C(=NOR₁)—COOH, inhibit incorporation of glycine into tumor tissue and exhibit slight antitumor activity.[3] This activity, in experimental animals, even though not pronounced, suggests that modifications in the structure of these compounds be made for pharmacological testing.

Aldehydes are not only versatile intermediates for further syntheses but are frequently very active biologically. Accordingly, the preparation of two α-alkyloximino aldehydes, R—C(=NOCH₂C₆H₅)—CHO, is described, namely R = CH_3— and R = $C_6H_5CH_2$—.

The most promising route appeared to depend on the reduction of the corresponding acid chlorides. To accomplish this, it was necessary to avoid reagents or conditions that would also attack the sensitive alkyloximino groups. Since it is impossible to obtain the chlorides of α-oximino acids, R—C(=NOH)—COCl, by conventional procedures[4] the oxime intermediate is not available for this type of study. The reduction was accomplished with tri-*t*-butyl-oxyaluminohydride according to the procedure of Brown and McFarlin.[5] The yields of aldehydes were very low and because of comparative instability were characterized by reoxidation to the carboxylic acid and a derivative. Insufficient material was obtained to permit biological screening.

EXPERIMENTAL

The preparation of α-benzyloximino acids and the conversion to the corresponding acid chlorides has been previously described.[6,7] A typical reduction was carried out as follows.

Eighteen and seven-tenths g. (0.089 mole) of α-benzyloximinopropionyl chloride was placed in a 500 ml. three neck flask equipped with magnetic stirrer, dropping funnel, and thermometer. Fifty ml. of dry tetrahydrofuran was added, and the solution was cooled to −78° in an acetone–Dry Ice bath. An equivalent amount of lithium tri-*t*-butoxyaluminohydride prepared in tetrahydrofuran[5] was added through the dropping funnel slowly with stirring and continued cooling so that the temperature never went above −70°. When addition was completed, the reaction mixture was allowed to come to room temperature and poured over crushed ice. Since filtration of the precipitate was difficult, the procedure of Brown and McFarlin[6] which was followed to this point, was modified slightly. The reaction mixture was made acid to litmus with dilute HCl at 0°. The mixture was extracted with five 50-ml. portions of ether. The ether was evaporated and the remaining oil, which gave positive Tollens' and Schiff tests, was treated with sodium bisulfite. A precipitate formed instantly. The addition product was dried in air and repeatedly washed with ether until the washings were clear. A portion of the product was treated with dilute HCl and the liberated aldehyde was extracted with ether, the ether evaporated, and the residual oil used to prepare derivatives and a portion of the aldehyde was oxidized to the parent acid in alkaline permanganate after the procedure outlined in McElvain.[8] Melting point of product 75–76°.

Derivatives of α-benzyloximinopropionaldehyde. Semicarbazone, $CH_{14}N_4O_2$, m.p. 189°. Calcd.: C, 56.31%, H, 5.98%;

(1) Paper number 19 in amino acid series. For number 18 see K. L. Hoy and W. H. Hartung, *J. Org. Chem.*, **23**, 967 (1958).

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