A Convenient Synthesis of Crystalline L-Threonolactone

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Many attempts to obtain L-threonolactone have resulted in poor yields of crude, syrupy material which had to be characterized by derivatives.[1,2] Reichstein, Grüssner, and Bosshard[2] isolated L-threonolactone as the brucine and quinine salts, using acetone L-ascorbic acid as a starting material. Gätzi and Reichstein[3] synthesized for the first time crystalline L-threonolactone directly from L-ascorbic acid in 32% yield. Subsequently, Gätzi and Reichstein,[4] in degradation studies of 3,5:4,6-di-*O*-ethylidene-L-glucitol, obtained very small yields of crystalline L-threonolactone. Later, Lucas and Baumgarten,[5] upon reduction of L-threuronic acid, were unable to obtain crystalline L-threonolactone by the Gätzi and Reichstein[3] isolation procedure and had to characterize it as the brucine salt. Also, Micheel and Peschke,[6] starting from L-threaric acid, obtained a poor yield of a syrup which, upon several months of standing, crystallized and was characterized as L-threonolactone. Hardegger *et al.*[7] obtained crystalline L-threonolactone by direct oxygenation of L-ascorbic acid; in this and one other publication,[8] no yields were given.

The original method of Reichstein, *et al.*[2] has now been simplified, and crystalline material of purity higher than reported[3,7] has been consistently obtained in better yield. L-Threonolactone was needed, in order to continue studies of the metabolism of L-ascorbic acid.[9]

EXPERIMENTAL

5,6-O-Isopropylidene-L-ascorbic acid was prepared from L-ascorbic acid and dry acetone in the presence of anhydrous cupric sulfate, m.p. 218–220°; yields of 95% can be obtained.[10]

Potassium 3,4-O-isopropylidene-L-threonate was prepared by a twenty-fold enlargement of the method of Reichstein, *et al.*[2] The 5,6-*O*-isopropylidene-L-ascorbic acid (86 g., 0.37 mole) was dissolved in 2000 ml. of carbon dioxide-saturated water and was cooled to 0°, causing part of the sugar compound to precipitate. To the resulting suspension, a solution of potassium permanganate (84 g., 0.53 mole) and potassium carbonate (70 g., 0.51 mole) in 2400 ml. of water was added dropwise during 2–3 hr., with constant mixing, the reaction mixture being kept at 0–5°. After reaction was complete (as noticed by lack of decolorization of the permanganate solution), the mixture was heated to 50° to coagulate manganese dioxide, which was filtered off. Two milliliters of ethanol were added and the solution was again filtered. The filtrate was evaporated to dryness with a rotary evaporator at 40°. The residue was extracted three to four times with 100-ml. portions of hot absolute ethanol, and solutions were pooled and evaporated *in vacuo* to about 25 ml. Crystallization was induced by the addition of 3 ml. of cold acetone and, upon evaporation of the solvents, 62 g. (0.29 mole, 78% yield) of a pale yellow solid was obtained. For this synthesis, it was not necessary to recrystallize the crude compound, which melted at 148–150° (m.p. recrystallized material 158°).

L-Threonolactone. A solution of 62 g. (0.29 mole) of the above potassium salt in 175 ml. of distilled water was passed through a 250 g. column of Amberlite IR-120(H), resin, analytical grade. The effluent and 300 ml. water wash were pooled, and the solution (*p*H 3–4) was evaporated to dryness *in vacuo* at 50°. The residue was dissolved in 200 ml. of hot absolute ethanol, and treated twice with 2.5 g. of activated carbon. Upon evaporation to dryness, 35 g. of a pale yellow syrup was obtained which was distilled as described by Gätzi and Reichstein.[3] The first fraction, 8 g. of yellow, nonviscous syrup, distilled at 100–130° (0.8 mm.); it had a sweet odor, and $[\alpha]_D^{21}$ + 10.3° (methanol, *c* 1.90). The main fraction distilled at 145–150° (0.25 mm.) (some decomposition towards the end), and consisted of 18 g. (0.15 mole, 52% yield) of a pale yellow syrup which rapidly solidified into a white crystalline material. The low boiling fraction, suspected to be the acetone derivative of L-threonic acid, when dissolved in 50 ml. of water, refluxed for 1 hr., and treated as above, gave about 4 g. of additional crystalline L-threonolactone. This increased the yield to 65%. Upon recrystallizing from dry ethyl acetate and washing with anhydrous ether,[3] 16 g. of L-threonolactone melting at 66–71° was obtained[11]; phenylhydrazide, m.p. 160–161°, $[\alpha]_D^{21}$ + 52.5° (methanol, *c* 0.73); brucine salt, m.p. 209–210° dec., $[\alpha]_D^{21}$ −19.7° (H_2O *c* 1.92).

A small portion of the lactone, recrystallized three more times, melted at 74–75°, $[\alpha]_D^{19}$ + 51.2 (methanol, *c* 1.54). Infrared (potassium bromide): 1775 cm.$^{-1}$ (γ-lactone), 3380 cm.$^{-1}$ (OH).

Anal. Calcd. for $C_4H_6O_3$: C, 40.63; H, 5.16. Found: C, 40.74; H, 5.37.

The compound gave a quantitative hydroxamic acid as-

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say for a glyconic acid lactone.[12] The best physical constants previously reported are: L-threonolactone, m.p. 74–76°,[8] $[\alpha]_D^{20}$ + 47.0° (methanol)[3]; phenylhydrazide, m.p. 161–161.5°, $[\alpha]_D^{21}$ + 48.6° (methanol)[3]; brucine salt, m.p. 209–210° dec., $[\alpha]_D^{22}$ −19.3° (H_2O).[3] Despite the high melting point given by Hardegger, *et al.*,[7] these authors report $[\alpha]_D$ −27.0° (H_2O) for the brucine salt, indicating the presence of optically active impurities; this suggests that the lower melting (65–68°) material obtained by Gätzi and Reichstein[3] was purer.

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Strong Analgesics. Some Ethyl 1-Alkyl-4-phenylpiperidine-4-carboxylates

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Some time ago, it was shown,[2] that when the *N*-methyl substituent of meperidine, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride, was replaced by lower alkyl groups the analgesic potency remained relatively constant although the toxicity gradually increased.

Recently it was reported[3] that replacement of the *N*-methyl substituent of meperidine by aralkyl groups other than benzyl gave compounds having significantly higher analgesic potency. It seemed of interest to us to see if relatively long alkyl groups would effect the same enhancement of analgesic potency.

Accordingly, analogs were prepared wherein the *N*-methyl substituent was replaced by various relatively long chain alkyl groups, both straight and branched.

The alkylation of ethyl 4-phenylpiperidine-4-carboxylate was accomplished using either alkyl halides or toluenesulfonates.

The pharmacological evaluation of these compounds for analgesic potency by the Bass, Vander Brook modification[4] of the D'Amour, Smith rat thermal stimulus method[5] will be reported more fully elsewhere, but a brief summary can be given here. It is apparent that the substituent on the nitrogen of meperidine can be extended to at least nine carbons without loss of any analgesic potency; in fact, the compounds having straight chains and one of the branched chain compounds are more potent than meperidine itself.

EXPERIMENTAL

Ethyl 1-heptyl-4-phenylpiperidine-4-carboxylate hydrochloride. A mixture of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (13.5 g., 0.05 mole), *n*-heptyl bromide (8.95 g., 0.05 mole), sodium carbonate (20 g.), and *n*-butyl alcohol (100 ml.) was refluxed with stirring for 24 hr. The solids were removed by filtration and a small piece of Dry Ice added to the filtrate to precipitate any secondary amine still present. The filtrate was then concentrated *in vacuo* on a steam bath and the residual oil taken up in ether. A small amount of precipitate was removed by filtration and ethereal hydrogen chloride was added to the filtrate. The product was collected and crystallized from ethyl acetate (150 ml.), then recrystallized from a mixture of benzene (65 ml.) and cyclohexane (65 ml.). There was obtained 14.3 g. (78.0%) of product, m.p. 146.4–149°.

2-Hexyl-p-toluenesulfonate. 2-Hexanol (255 g., 2.5 moles) and pyridine (595 g., 7.5 moles) were stirred in an open beaker and cooled to 0°. *p*-Toluenesulfonyl chloride (858 g., 4.5 moles) was added portionwise over 3 hr. at such a rate as to keep the temperature at about 15°. When the addition was completed, the reaction mixture was allowed to reach room temperature. The unchanged *p*-toluenesulfonyl chloride was hydrolyzed by addition of 150 ml. of water and 200 ml. of pyridine. After hydrolysis was completed, concd. hydrochloric acid was added, the aqueous layer was separated, and the organic layer was washed with water, dilute sodium bicarbonate solution, and water again. Traces of water were removed from the organic layer by heating at 50–60° at reduced pressure, first with a water pump and then with a mechanical pump. There was obtained 533 g. (82%) of yellow oil which was used without further purification.

Ethyl 1-(2-hexyl)-4-phenylpiperidine-4-carboxylate. Methane sulfonate. Ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (1700 g., 6.3 moles) was dissolved in 2.5 l. of water. The solution was made basic with 35% aqueous sodium hydroxide, extracted with ether, the extract dried over anhydrous sodium sulfate, and concentrated to an oil. 2-Hexyl-*p*-toluenesulfonate (768 g., 3.0 moles) was added all at once. The reaction mixture turned into a thick magma after stirring for 3 hr. at room temperature. Heating on the steam bath caused the mixture to liquify, then resolidify after 1 hr. Heating was continued for 1 hr. more and the mixture allowed to stand overnight. Three liters of water was added to the solid reaction mixture, which was heated on the steam bath until solution was complete. The cooled solution was extracted with ether several times. A 750-ml. portion of water was added to the ether extracts and 252 ml. of concd. hydrochloric acid added with cooling. In 15 min. the product precipitated. After drying there was obtained 848 g. (80%) of ethyl 1-(2-hexyl)-4-phenylpiperidine-4-carboxylate hydrochloride, m.p. 162–164. A 1098-g. sample (3.1 moles) of the above hydrochloride was dissolved in 3 l. of water, made basic with 35% sodium hydroxide, and extracted with benzene. The extract was concentrated *in vacuo* and the oily residue dissolved in 250 ml. of isopropyl alcohol and 4 l. of ether. Methanesulfonic acid (328 g., 3.41 moles) was added with cooling and stirring. The product

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