SYNTHESIS OF 4-OXODODECANOIC AND 4-OXODODECANEDIOIC ACIDS

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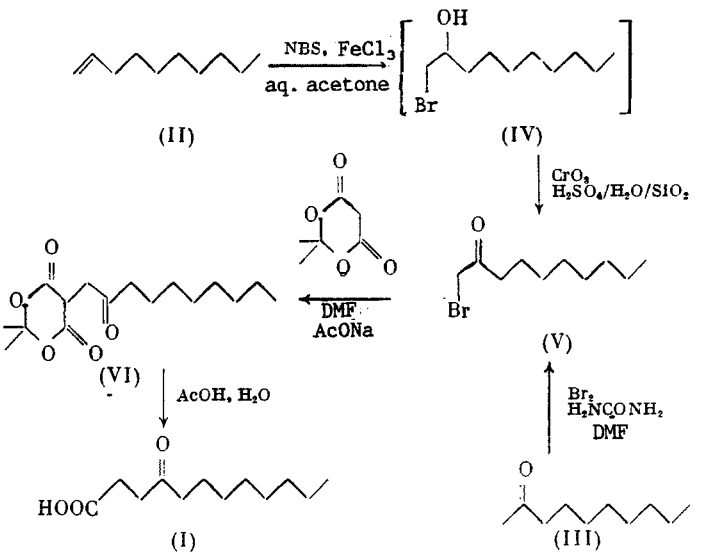
A short synthesis is described for 4-oxododecanoic acid starting from 1-decene or 2-decanone and of 4-oxododecanedioic acid from the methyl ester of 9-oxodecanoic acid.

4-Oxododecanoic acid (I) is a natural product [1] and is used as a starting reagent for the preparation of several oxygen and nitrogen heterocycles [2, 3]. We carried out a brief synthesis of this compound from 1-decene (II) or 2-decanone (III) by the following scheme:



The bromohydroxylation of 1-decene (II) by NBS in aqueous acetone by the action of catalytic amounts of $FeCl_3$ with the subsequent oxidation of intermediate bromohydrin (IV) by the Jones reagent in the presence of SiO_2 gave bromoketone (V). The addition of SiO_2 and $FeCl_3$ facilitated stirring of the reaction mixture and provided for a stable yield of reaction product (V). The reaction of bromoketone (V) with Meldrum's acid in aqueous DMF containing sodium acetate led to C-alkylation product (VI), which was cleaved by aqueous acetic acid to desired ketoacid (I). Product (VI) was also synthesized by the regioselective bromination of 2-decanone (III) in DMF in the presence of urea [4] with subsequent treatment of intermediate bromoketone (V) with Meldrum's acid and sodium acetate under the conditions described above. The transformations (II) → (V) and (III) → (VI) were carried out in a single flask without isolation of intermediate bromohydrin (IV) in the former case and of bromoketone (V) in the latter. The total yield of ketoacid (I) was 29% relative to (II) or 34% relative to (III).

Analogously, the methyl ester of 9-oxodecanoic acid (VII) was transformed to intermediate bromoketone (VIII) and the product of the alkylation of Meldrum's acid (IX) to give another natural product, namely, 4-oxododecanoic acid (X) [5] in 38% overall yield

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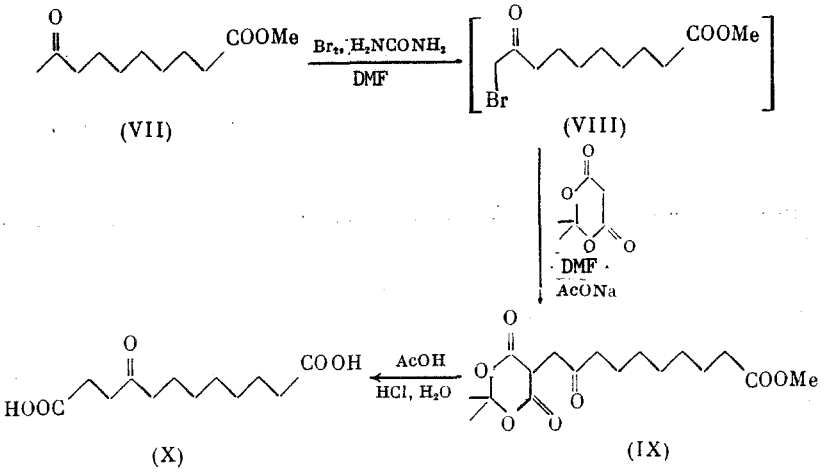

Ketoacids (I) and (X) were identified relative to their melting points and IR and PMR spectra.

EXPERIMENTAL

The IR spectra were taken using KBr pellets on a UR-20 spectrometer. The PMR spectra were taken on a Tesla BS-467 spectrometer at 60 MHz with HMDS as the internal standard and a Bruker WM-250 spectrometer. The thin-layer chromatography was carried out on Silufol UV-254 using 4:1 benzene–ethyl acetate (EA) with development by iodine vapor.

1-Bromo-2-decanone (V). A sample of 5.4 g (30.33 mmoles) N-bromosuccinimide was added with stirring and water cooling to a mixture of 4.1 g (29.23 mmoles) 1-decene (II), 0.05 g $FeCl_3 \cdot 6H_2O$, and 1 ml water in 25 ml acetone and stirred for an additional 30 min. Then, 1 g SiO_2 (100/160 μ) was added followed by the addition of a solution of 3 g (30 mmoles) CrO_3 in 2 ml concentrated sulfuric acid and 6 ml water over 15 min with vigorous stirring and water cooling. Stirring was continued for an additional 1.5 h at about 20°C. The reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with water and aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. The residue was distilled in vacuum to give 5 g (72.7%) 1-bromo-2-decanone (V), bp 148-151°C (15 mm), n_D^{25} 1.4635. PMR spectrum in CCl_4 (δ, ppm, J, Hz): 0.83 m (CH_3), 1.32 m ($(CH_2)_6$), 2.56 t (CH_2CO, J = 7), 3.75 s ($COCH_2Br$).

2,2-Dimethyl-5-(2-oxodecyl)-1,3-dioxane-4,6-dione (VI). A sample of 3 g (22.04 mmoles) finely ground $AcONa \cdot 3H_2O$ was added to a mixture of 3.2 g (22.20 mmoles) Meldrum's acid and 4 g (17.01 mmoles) bromoketone (V) in 10 ml DMF and stirred for 24 h at about 20°C. The mixture was diluted with water, treated with excess potassium carbonate, and extracted with ether. The aqueous alkaline solution was acidified by a solution of one part water and one part concentrated hydrochloric acid and reextracted with ether. The extract was dried over $MgSO_4$ and evaporated in vacuum to give 3.4 g (67%) (VI), mp 58-60°C (low-temperature crystallization from ether at −70°C), R_f 0.62. PMR spectrum in $CDCl_3$ (δ, ppm, J, Hz): 0.86 t (CH_3, J = 7.5), 1.25 br. s ($(CH_2)_5$), 1.58 m (CH_2), 1.82 s ($2CH_3$), 2.49 t ($COCH_2$, J = 7.5), 3.27 d (>CH—$\underline{CH_2}$, J = 5), 3.80 t (CH, J = 5). Found: C, 64.42; H, 8.86%. Calculated for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78%.

A sample of 1.5 ml (29.47 mmoles) bromine was added dropwise with stirring and ice cooling to a mixture of 4.7 g (30.07 mmoles) 2-decanone and 2.5 g (41.63 mmoles) urea in 10 ml DMF and maintained for 1.5 h until the bromine disappeared. Then, 4.4 g (30.53 mmoles) Meldrum's acid and 9 g (66.13 mmoles) $AcONa \cdot 3H_2O$ were added and stirred for 24 h at about 20°C. The above treatment gave 5.1 g (57%) (VI), mp 59-60°C.

4-Oxododecanoic Acid (I). A mixture of 5.1 g (VI), 5 ml water, and 20 ml acetic acid was heated at reflux for 5 h and evaporated in vacuum. The residue was treated with water and the precipitate was filtered off, washed with water, and dried in the air to give 2.2 g (60%) ketoacid (I), mp 77-78°C (low-temperature crystallization from ether at −70°C) [6], R_f 0.48. IR spectrum (ν, cm^{-1}): 1680 (CO_2H), 1700 (CO). PMR spectrum in $CDCl_3$ (δ, ppm, J, Hz): 0.85 br. s (CH_3), 1.24 br. s ($(CH_2)_5$), 1.55 m (CH_2), 2.42 t ($COCH_2$, J = 7.5), 2.65 m ($2CH_2$).

4-Oxododecanedioic Acid (X). A sample of 0.8 ml (15.70 mmoles) bromine was added dropwise slowly with stirring and water cooling to a mixture of 3 g (14.97 mmoles) methyl ester of 9-oxodecanoic acid (VII) [7], 2.5 g (41.67 mmoles) urea, and 7 ml DMF and stirred for about 2 h until the bromine disappeared. Then, 5 g (34.69 mmoles) Meldrum's acid and 5 g

(36.76 mmoles) $AcONa \cdot 3H_2O$ were added consecutively and stirred for 24 h at about 20°C. The reaction mixture was diluted with water and treated with excess sodium carbonate. The impurities were extracted with ether. The aqueous alkaline solution was acidified with a solution of one part water and one part concentrated hydrochloric acid and extracted with EA. The extract was dried over $MgSO_4$ and evaporated in vacuum. The residue consisted of alkylation product (IX). This product was stirred with 30 ml acetic acid and 5 ml water and heated at reflux for 3 h. Then, 3 ml concentrated hydrochloric acid was added and the mixture was heated at reflux for an additional 3 h and evaporated in vacuum. The residue was treated with 10-15 ml of water, held at 0°C for 24 h, filtered, washed with water and dried in the air to give 1.4 g (38%) ketodiacid (X), mp 106-107°C (from EA) [5], R_f 0.74 (ether as the eluent, development of the spot with saturated aqueous $KMnO_4$). IR spectrum (ν, cm^{-1}): 1698 (CO_2H), 1703 (CO). PMR spectrum in CD_3OD (δ, ppm): 1.32 m ($(CH_2)_5$), 2.06-2.87 m ($2CH_2CO$, $2CH_2CO_2H$). The yield of ketodiacid (X) was 1.1 g (30%) when 0.8 ml (15.70 mmoles) bromine, 1.5 g (25.0 mmoles) urea, 5 g (36.76 mmoles) $AcONa \cdot 3H_2O$, and 2.2 g (15.26 mmoles) Meldrum's acid were used to treat 3 g (14.97 mmoles) ketoester (VII).

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PREPARATION OF α-DEUTERATED L-AMINO ACIDS USING E. coli CELLS CONTAINING TRYPTOPHANASE

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A preparative method has been developed to obtain a series of α-deuterated L-amino acids with high chemical yields and quantitative optical yields by stereospecific isotope exchange in D_2O by the action of E. coli cells with high tryptophanase action.

The study of the mechanisms of biological transformations of natural amino acids is markedly facilitated by the use of isotope-labelled substrates, in particular, α-deuterated derivatives. The chemical methods for the preparation of α-deuterated amino acids lead to the formation of racemic products [1]. Methods using the diastereomeric properties of complexes of transition metals with Schiff bases of amino acids [2, 3] permit the preparation of α-deuterated L-amino acids with high optical purity.

Enzymatic methods have been reported for the introduction of hydrogen isotopes into the α-positions of natural amino acids by stereospecific isotope exchange in water enriched by the corresponding isotope. This process is catalyzed by pyridoxal-5'-phosphate-dependent enzymes specific for the given amino acid [4, 5]. These methods require only mild conditions without the need for auxiliary steps and have high steric specificity. A significant disad-

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