"Isolipoic Acid", a New Isomer of α-Lipoic Acid

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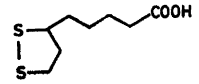
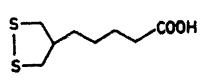
Several homologues and analogues of α-lipoic acid (I) have been prepared and tested for biological activity (*cf.* Refs.[1,2]). The isomer II has, however, not been synthesized before despite its possible biological interest. In this note we want to report the successful synthesis of δ-(1,2-dithiolane-4)-valeric acid, or "isolipoic acid" (II) according to the scheme given below.



I

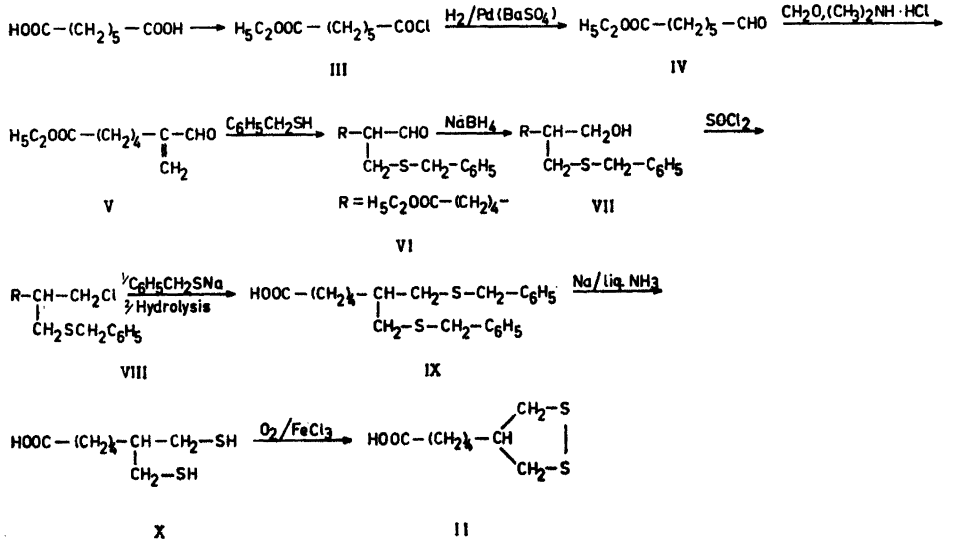


II

The synthesis of the unsaturated aldehyde V, which is the crucial intermediate, was achieved by a Mannich condensation on IV. The over-all yield of "isolipoic acid" based upon 6-carbethoxycaproyl chloride (IV) was 7.1 %. The UV-spectra of I and II are almost identical. II has a somewhat higher m.p. (68–70°C) than I [m.p. 61–62°C (racemic)]. Further studies of "isolipoic acid" and related compounds are in progress.

Experimental. Ethyl 6-formylcaproate (IV) was prepared by a Rosenmund reduction of III. Hydrogen was bubbled through a vigorously stirred mixture of 64.3 g (0.311 mole) of 6-carbethoxycaproyl chloride[3] (III), 5.6 g of 5 % Pd-$BaSO_4$-catalyst,[4] 0.2 ml of quinoline-sulfur poison[5] and 200 ml of dry xylene at 130–140°C. The reaction was followed by titration of the evolved hydrogen chloride, using 5 N sodium hydroxide solution. After 2½ h, 92 % of the theoretical amount of hydrogen chloride was evolved and the reaction stopped. After cooling, the reaction mixture was filtered by suction, the xylene removed *in vacuo* and the residue distilled under nitrogen atmosphere. 37.1 g of IV was collected. Yield 69.1 %. B.p. 80–81°C/1.2 mm Hg. n_D^{25} 1.4304. (Found: C 62.32; H 9.36. Calc. for $C_9H_{16}O_3$ (172.23): C 62.76; H 9.36).

α-(ω-Carbethoxybutyl)-acrolein (V). A mixture of 36.0 g (0.209 mole) of ethyl 6-formylcaproate (IV), 19.6 g (0.240 mole) of dimethylamine hydrochloride and 23.2 g (0.255 mole) of formaldehyde (33 %) was refluxed at 110–120°C under nitrogen atmosphere for 2½ h. After cooling, the reaction mixture was extracted with ether. After drying with $MgSO_4$ the ether was removed *in vacuo* and the product distilled under nitrogen atmosphere. 24.0 g of V was collected at 75–77°C/0.6 mm Hg.



Yield 62.2 %. n_D^{25} 1.4506. (Found: C 64.98; H 8.71. Calc. for $C_{10}H_{16}O_3$ (184.24): C 65.19; H 8.75). The NMR-spectrum was consistent with the proposed structure.

ε,ε-Di-(benzylmercaptomethyl)-caproic acid (IX). A mixture of 21.0 g (0.114 mole) of α-(ω-carbethoxybutyl)-acrolein (V), 14.2 g (0.114 mole) of benzyl mercaptan and ten drops of piperidine was stirred in nitrogen atmosphere for 18 h at room temperature. The reaction mixture was then dissolved in ether, the solution washed with dilute hydrochloric acid and with water until neutral reaction. After drying with $MgSO_4$, the ether was removed *in vacuo* and the residue heated to 120°C/10 mm Hg under nitrogen. Some unreacted benzyl mercaptan was thereby removed. The residue, 28.0 g, of crude VI (0.091 mole), was dissolved in 100 ml of absolute ethanol and 0.95 g (0.025 mole) of sodium borohydride was added in portions during one hour. After another hour, the mixture was poured into an excess of water, acidified with hydrochloric acid and extracted with ether. After washing with water until neutral reaction, the ether solution was dried with $MgSO_4$. The product, VII (25.0 g), was isolated as crude material by vacuum evaporation of the ether. This amount (0.081 mole) was dissolved in 40 ml of dry benzene and added dropwise to a mixture of 12.3 g (0.103 mole) of thionyl chloride, 20 ml of dry benzene, and ten drops of pyridine. The mixture was refluxed for one hour and then poured into an excess of water and extracted with ether. The ether solution was washed with sodium bicarbonate solution and water and finally dried with $MgSO_4$. After removal of the solvents, 25.7 g (0.078 mole) of crude VIII remained. A solution of sodium mercaptide was prepared from 1.89 g (0.082 mole) of sodium, 10.2 g (0.082 mole) of benzyl mercaptan, and 100 ml of absolute ethanol. To this mixture was added the solution of crude VIII, 25.7 g, in 40 ml of absolute ethanol. This reaction mixture was stirred in a nitrogen atmosphere at room temperature for 18 h and then refluxed for 4 h. Precipitated sodium chloride (4.4 g, 96.5 %) was filtered off and the filtrate poured into an excess of water and acidified with sulfuric acid. The mixture was extracted with ether and after washing with water the ether solution was dried with $MgSO_4$. The ether was evaporated, giving the residual crude ethyl ester of IX, 29.5 g (0.071 mole), which was subsequently dissolved in 200 ml of absolute ethanol, and 8.41 g (0.150 mole) of potassium hydroxide in 10 ml of water was added. After 42 h at room temperature, the mixture was poured into an excess of water, acidified with sulfuric acid and extracted with ether. After drying with $MgSO_4$ and evaporation of the solvents, 25.2 g (91.5 %) of crude IX remained as a viscous brown-yellow oil. No attempts were made to purify this product further.

δ-(1,2-Dithiolane-4)-valeric acid (II). 25.2 g (0.065 mole) of crude IX dissolved in 90 ml of dry toluene was added dropwise to about 500 ml of liquid ammonia at about −50°C. At the same time, sodium, cut into small pieces, was added until a permanent dark blue colour remained for 30 min. The reaction mixture was vigorously stirred. Excess sodium was destroyed with ammonium chloride and the ammonia allowed to evaporate. Water was added to the residue, the organic layer was discarded, the water solution acidified with hydrochloric acid and extracted with ether. After drying and evaporating of the ether the crude mercapto acid X remained. This product was dissolved in 500 ml of water with some ammonia added, the pH adjusted to 7−8 and a few drops of dilute $FeCl_3$-solution was added. Air was passed through this solution for 16 h. The solution was acidified with hydrochloric acid and extracted with 250 ml of chloroform. The yellow chloroform extract was dried with $MgSO_4$ and the solvent removed *in vacuo* at room temperature. The residue was a yellow oil, 12 g. This oil was extracted with petroleum ether at about 60°C from which solution the product crystallized. Recrystallization from petroleum ether gave 4.5 g of lustrous, yellow flakes of pure II, m.p. 68−70°C. Yield 33.8 %. (Found: C 46.98; H 6.91; S 30.98; equiv.wt. 203.4. Calc. for $C_8H_{14}S_2O_2$ (206.33): C 46.57; H 6.84; S 31.08; equiv.wt. 206.33). (λ_{max} 333.5 mμ (chloroform), ε_{max} 149).

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