# NEW METHOD OF SYNTHESIS OF BIOLOGICALLY IMPORTANT DERIVATIVES OF PELARGONIC ACID

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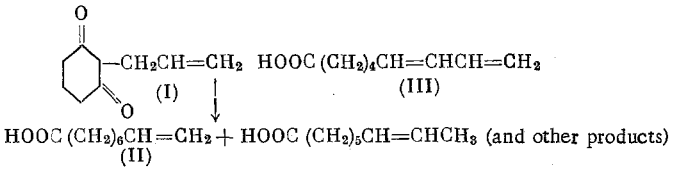
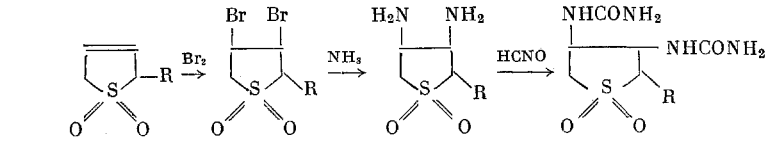
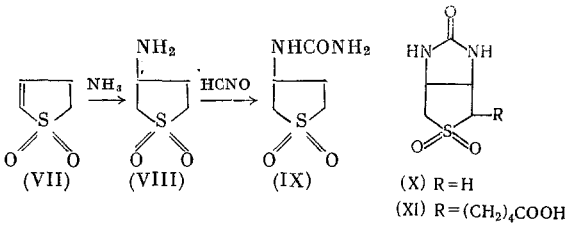
It is known that substituted pelargenic acids, containing amino and keto groups in the 7- and 8-positions, show biotin activity and nowadays are considered as bioprecursors of biotin [1].

In order to study further the biologically important derivatives of pelargonic acid we attempted to develop new simple methods for their synthesis based on accessible starting substances. In the first place 2-allyldihydroresorcinol (I), which according to the data [2] is easily cleaved to non-8-enoic acid (II) on heating with hydrazine hydrate and alkali in diethylene glycol, was taken for this study. It was proposed to use non-8-enoic acid in the synthesis of various compounds with the carbon skeleton of biotin, in particular nona-6,8-dienoic acid (III). The latter might be, for example, reacted with sulfur dioxide and the sulfolane (V) formed from this converted via a series of steps into sulfobiotin (XI). However, this study was discontinued after we discovered by the method of gas–liquid chromatography (GLC) the heterogeneity of the non-8-enoic acid, which contained as impurities considerable quantities of other isomeric acids




An attempt to add an imidazoline ring to the double bond of the sulfol-3-ene (IV) also proved to be unsuccessful. It yielded on successive treatment with bromine, ammonia, and potassium cyanate the 3,4-diureidosulfolane (VI), which could not be converted into the imidazolidinone (X). The structure of the diureide (VI) was confirmed by the similarity of its IR spectrum with the spectrum of 3-ureidosulfolane (IX), obtained by the addition of ammonia to the sulfol-2-ene (VII) and carbamidation of the intermediate 3-aminosulfolane (VIII)




The second possibility for the construction of the carbon skeleton of biotin examined by us related to the use as starting substances of ketones of the Mannich type (XII) and (XIII). In the hope of obtaining 3-ketotetrahydrothiophene (XIV) from 4-dimethylaminobutan-2-one (XII) we heated it with elementary sulfur in dioxane. The reaction proceeded with the liberation of ammonia and led to the formation of a com-

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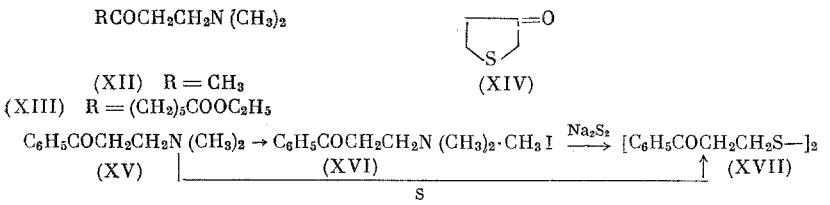
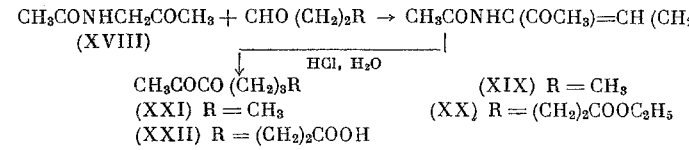
plex mixture of unidentified products. Under similar conditions β-dimethylaminopropiophenone (XV) formed in low yield the disulfide (XVII), which could also be obtained by the action of $Na_2S_2$ on the methiodide (XVI)




An attempt to obtain biologically important derivatives of pelargonic acid on the basis of the crotonic condensation of aldehydes with acetamidoacetone (XVIII) proved to be more successful. The latter compound under the influence of alkaline catalysts condensed easily with butyraldehyde and with the ester of adipic half aldehyde to form the unsaturated ketones (XIX) and (XX), which on acid hydrolysis gave the corresponding α-diketones (XXI) and (XXII). The diketo acid (XXII) was identical in all respects to 7,8-diketopelargonic acid, synthesized by Japanese investigators, starting from 8-ketopelargonic acid [3]




According to the experimental data, carried out by us on the yeast (Saccharomyces cerevisiae), 7,8-diketopelargonic acid possesses 18% of the activity of natural biotin.

## EXPERIMENTAL

The Reductive Cleavage of 2-Allyldihydroresorcinol (I). On reductive cleavage of (I), according to [2], a mixture of isomeric octenoic acids was obtained with bp 124-126° (5 mm); $n_D^{20}$ 1.4450, the hydrogenation of which over $PtO_2$ in alcohol at atmospheric pressure and 20°C gave pelargonic acid, and the oxidation with permanganate in aqueous solution at 20° gave a mixture of suberic, pimelic, adipic, and lower dicarboxylic acids.

The identification of the above acids was carried out by GLC according to the earlier published method [4].

Preparation of 3,4-Diureidosulfolane (VI). A mixture of 2 g of 3,4-dibromosulfolane (mp 141-143° [5]) and 50 ml of 28% ammonia solution was left for 24 h at ~20°, then filtered and evaporated to dryness in vacuum. The residue was dissolved in 6 ml of water, 1.04 g of potassium cyanate was added, and 34% HCl to pH 6-6.5. The solution was heated for 20 min at 100°, then cooled to ~20° and the precipitate, which separated, filtered off, 0.45 g (31%) of (VI) was obtained with mp 246-250° (with decomp.). After recrystallization from water the melting point was raised to 255-256°, $R_f$ (here and later thin-layer chromatography on Stahl silica gel G, detection of spots by iodine vapor) 0.50 in the system acetone–water 4:1. IR spectrum (here and later KBr disc)*: 3400, 3320, 1657, 1605, 1550, 1370, 1297, 1260, 1115, 905, 825, and 770 $cm^{-1}$. Found %: C 30.49, 30.63; H 5.15, 5.14; N 24.01, 23.79; S 13.01, 13.21. $C_6H_{12}O_4N_4S$. Calculated %: C 30.50; H 5.08; N 23.73; S 13.55.

Preparation of 3-Ureidosulfolane (IX). A mixture of 2 g of sulfol-2-ene (VII) (mp 47 to 49° [5]) and 50 ml of 28% ammonia was left for 24 h at ~20° and then evaporated to dryness under vacuum. The residue was dissolved in 5 ml of water and 1.1 g of KCNO and 1.5 ml of 34% HCl were added. After heating for 20 min at 100° and cooling to 20° the precipitate, which separated, was filtered off. 0.86 g (35%) of (IX) was obtained with mp 184-186°. On recrystallization from water the melting point was raised to 197-200°. The yield of (IX) was 0.6 g (25%) with $R_f$ 0.61 in the system acetone–water 4:1. IR spectrum: 3360, 3200, 1650, 1615, 1535, 1375, 1300, 1275, 1115, 905, 820, and 765 $cm^{-1}$. Found %: C 34.01, 33.91; H 6.61, 6.60; N 15.65, 15.91; S 17.54, 17.57. $C_5H_{10}O_3N_2S$. Calculated %: C 33.70; H 6.72; N 15.73; S 17.97.

*IR spectra determined on DS-301 spectrophotometer.

Preparation of Disulfide (XVII). A mixture of 1 g of β-dimethylaminopropiophenone methiodide (XVI) and 0.41 g of $Na_2S_2$ in 8 ml of water was boiled for 1 h. An oil, which on standing partially crystallized, was extracted from the cooled solution by ether. After pressing out the crystals on a filter and washing with ether 0.22 g of (XVII) was obtained, mp 84-85°. Found %: C 60.81, 60.95; H 5.45, 5.65; S 9.25, 9.37. $C_{18}H_{18}O_2S_2$. Calculated %: C 60.54; H 5.45; S 9.69.

Reaction of β-Dimethylaminopropiophenone (XV) with Sulfur. A mixture of 3.5 g of (XV) [6] and 1.28 g of sulfur in 20 ml of dioxane was boiled for 4 h, cooled, filtered and treated with dilute HCl until acid to Congo Red. Ether extraction gave 2 g of oil, which was subjected to chromatography on $Al_2O_3$ (activity II). The semicrystalline mass eluted with benzene was pressed on a filter and washed with ether. 0.1 g of (XVII) was obtained with mp 84-85° which gave no depression of melting point on admixture with an authentic sample (mp 84-85°).

Condensation of Acetamidoacetone (XVIII) with Butyraldehyde. A mixture of 4.6 g of (XVIII) (bp 115-116° at 4 mm; $n_D^{18}$ 1.4516 [7]), 2.9 g of butyraldehyde, 4-5 drops of piperidine, and 2 drops of pyridine in 20 ml of alcohol was boiled for 5 h. After removal of the solvent the residue was distilled in vacuum. 6 g of oil was obtained with bp 130-136° (4 mm); $n_D^{05}$ 1.4840, which on standing partially crystallized. After pressing the crystals on a filter and washing with n-heptane 3.7 g (53%) of (XIX) was obtained with mp 67-69°, $R_f$ 0.175 in the system acetone–water, 4:1. $\lambda_{max}$ 244 mμ (ε 4070). Found %: C 64.04, 64.04; H 9.06, 9.05; N 8.39, 8.38. $C_9H_{15}O_2N$. Calculated %: C 63.90; H 8.87; N 8.27.

Preparation of 2,3-Diketoheptane (XXI). A solution of 1 g of (XIX) in 20 ml of dilute HCl (1: 1) was heated for 2 h at 100°, then cooled and the oil extracted with ether, on distillation of this oil in vacuum 0.46 g (61%) of (XXI) was obtained, bp 44-45° (10 mm); $n_D^{19}$ 1.4150; $R_f$ 0.82 in the system ethyl acetate–heptane, 1: 1. (XXI) gave a dark coloration with $FeCl_3$. According to the literature data [8]: bp 46° (13 mm); $n_D^{18}$ 1.4150.

Condensation of Acetamidoacetone with the Ethyl Ester of Adipic Half Aldehyde. A mixture of 1.16 g of (XVIII), 1.58 g of the ethyl ester of adipic half aldehyde (bp 115-117° at 13 mm; $n_D^{20}$ 1.4310 [9]), 0.05 ml of acetic acid and 0.1 ml of piperidine in 6 ml of methanol was heated for 2.5 h at 50°. After removal of the solvent the residue was distilled in vacuum. 1.18 g (46%) of (XX) was obtained, bp 192-194° (3 mm); $n_D^{17}$ 1.4760; $R_f$ 0.70 in the system acetone–heptane, 4: 1. $\lambda_{max}$ 240 mμ (ε 4060). Found %: N 5.74, 5.91. $C_{13}H_{21}O_4N$. Calculated %: N 5.49.

Preparation of 7,8-Diketopelargonic Acid (XXII). A solution of 0.48 g of (XX) in 10 ml of dilute HCl (1: 1) was heated for 1 h at 100°, then cooled and the 0.22 g of semicrystalline mass extracted with ether. On lowering the crystallization temperature 80 mg (20%) of (XXII) separated from ether (–78°), mp 51-52°, $R_f$ 0.64 in the system acetone–heptane, 4: 1. (XXII) did not depress the melting point in admixture with an authentic sample. According to literature data [3]: mp 51-52°.

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## CONCLUSIONS

1. The reductive cleavage of 2-allyldihydroresorcinol under the action of hydrazine hydrate and alkali is accompanied by migration of the double bond and leads to a mixture of isomeric octenoic acids.

2. The synthesis of 7,8-diketopelargonic acid is accomplished by the reaction of acetamidoacetone with the ethyl ester of adipic half aldehyde and subsequent hydrolysis of the crotonic condensation product.

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