TABLE I

Substituents	$R_1 = R_2 = CH_3$	$R_1 + R_2 = (CH_2)_5$
Diethyl malonate	84% yield[6] b.p. 83° (18 mm.)–85° (19 mm.) (lit. 196.5°)[5]	50% yield[7] b.p. 74–77° (0.3 mm.) (lit. 105–106° 5 mm.)[7]
Malonic acid	90% yield m.p. 191–192° (dec.) (lit. 193–194°, dec.)[5]	70% yield m.p. 170–171° (dec.) (lit. 176°, dec.)[8]
Malonyl chloride	76% yield b.p. 156–159° (lit. 165°)[9]	68% yield b.p. 67–69° (0.7 mm.)
α-Deuterated acid	58% yield (from the malonyl (chloride) b.p. 151.8–152.2° (lit. 153.5–154.4°)[10] 1.07 atoms of deuterium per molecule of acid[12]	53% yield (from the malonyl chloride) b.p. 90.0–90.5° (1 mm.) (lit. 232.5°)[11] 1.05 atoms of deuterium pr molecule of acid[13]

EXPERIMENTAL

Hydrolysis of malonic ester.[5] The malonic ester (1 mole) is refluxed for 20 hr. with a 25% alcoholic potassium hydroxide (4 moles) solution. The reaction mixture is cautiously distilled and 60–75% of the alcohol is collected. Water (a volume equal to one-half of the original volume of alcohol in the reaction mixture) is added to the residue and the distillation is continued until all of the alcohol is removed. The residue is extracted with ether to remove any unreacted ester.

The residue is cooled and cautiously acidified with concentrated hydrochloric acid. The acidified mixture is extracted with ether. The ether is evaporated from the solution and the residue is dried in a vacuum dessicator.

Preparation of malonyl chloride. A mixture of the malonic acid 1 mole) and thionyl chloride (5 moles) is refluxed for 20 hr The excess thionyl chloride is distilled from the reaction m ixture and the crude acid chloride is distilled.

Hydrolysis of malonyl chloride with heavy water and decarboxylation of the deuterated malonic acid. A mixture of the malonyl chloride and 99.5% deuterium oxide (15% excess) is cautiously refluxed for 2 hr. The mixture is heated to 30° below the melting point of the malonic acid to remove the excess water. The residue is cautiously heated to 15–20° degrees above the melting point of the malonic acid until no more gas is evolved.

The crude α-deuterated acid is dissolved in hot water and the solution is refluxed to exchange the deuterium of the carboxylic acid group. The α-deuterated acid is separated from the water and distilled.

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(13) The acid was converted to the methyl ester which was analyzed for deuterium by densities. A mixture (d^{25}_4 0.9753) was prepared from 2.20 g. of the deuterated ester and 7.79 g. of the undeuterated ester (d^{25}_4 0.9736).

An N-Dialkylaminoalkylpyrimidine[1]

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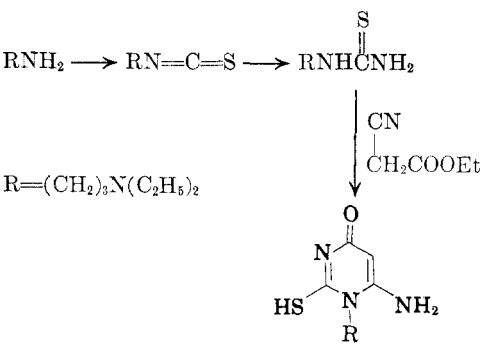
A sample of 6-amino-1-(3-diethylaminopropyl)-2-mercapto-4-(1H)pyrimidone has been prepared by the following sequence.



EXPERIMENTAL

3-Diethylaminopropyl isothiocyanate. To a stirred mixture of 20 ml. of water and 7.6 g. (0.1 mole) of carbon disulfide in an ice bath, 13.0 g. (0.1 mole) of 3-diethylaminopropylamine was added during 45 min. After the addition the mixture was stirred at that temperature for 0.5 hr. The ice bath was removed and 10.9 g. (0.1 mole) of ethyl chlorocarbonate was added to the mixture over a period of 1 hr. The solid dithiocarbamate derivative which had earlier separated gradually went into solution at this stage. After stirring for 30 min. more the solution was transferred to a separatory funnel and basified with a slight excess of concentrated aqueous caustic soda solution. The upper oily layer was separated and the aqueous portion was extracted once with ether. The combined organic layers were dried with magnesium sulfate and ether was removed at atmospheric pressure. The residue was fractionally distilled *in vacuo*, yielding 10 g. (58%) of colorless liquid boiling at 95° (3.5 mm.), (n^{25}_D 1.4968).

Anal. Calcd. for $C_8H_{16}N_2S$: C, 55.81; H, 9.30; N, 16.28; S, 18.60. Found: C, 55.51; H, 9.46; N, 16.30; S, 18.40.

3-Diethylaminopropylthiourea. A mixture of 10 ml. of concentrated ammonium hydroxide solution and 10 g. (0.058 mole) of 3-diethylaminopropylisothiocyanate was heated on a steam bath for 30 min., cooled, and treated with 10 ml. of acetone. On scratching, the thiourea was obtained as a white crystalline solid (10 g., 91%) melting at 97°. After recrystallization from acetone, the thiourea melted at 98°.

Anal. Calcd. for $C_8H_{19}N_3S$: C, 50.79; H, 10.06; N, 22.22; S, 16.92. Found: C, 50.87; H, 9.93; N, 22.20; S, 17.00.

6-Amino-1-(3-diethylaminopropyl)-2-mercapto-4-(1H)-pyrimidone. 3-Diethylaminopropylthiourea (9.5 g., 0.05 mole) was dissolved in a solution of sodium ethoxide in ethanol pre-

(1) This work was supported by Public Health Service Grant C-2189, to the University of Pennsylvania.

pared from 1.85 g. (0.08 mole) of sodium in 25 ml. of absolute ethanol. To the cooled solution, 6 g. (0.053 mole) of ethyl cyanoacetate was added and the mixture was refluxed for 2 hr. After the period was over the mixture was cooled, 30 ml. of water was added and the resulting solution was neutralized with an equivalent quantity of acetic acid. The pyrimidine derivative (9.5 g., 74% yield) was collected and washed with water. Recrystallization from ethyl alcohol yielded white shining crystals melting at 215–216°.

Anal. Calcd. for $C_{11}H_{20}ON_4S$: C, 51.56; H, 7.81; N, 21.88; S, 12.50. Found: C, 51.66; H, 7.69; N, 21.90; S, 12.05.

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Isotopically Labeled β-Aminopropionitrile[1]

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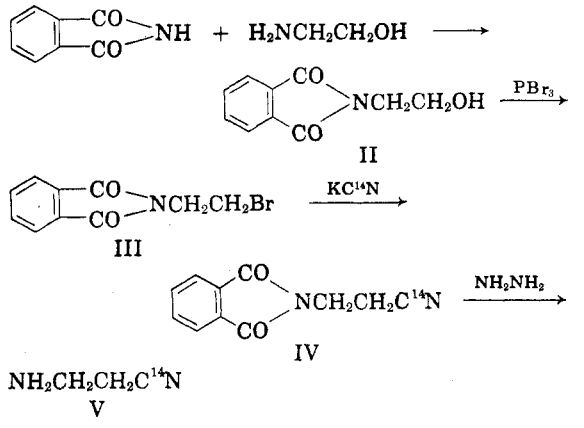
Following the demonstration that β-(N-γ-L-glutamyl)aminopropionitrile (I) is the natural causative agent of the skeletal deformities produced in rats by *Lathyrus odoratus* seeds,[3] it was readily established that the toxicity was due to the β-aminopropionitrile (BAPN) portion of the molecule.[4–6] As a possible aid in studying the mechanism by which BAPN causes the breakdown of mesenchymal tissues, isotopically labeled material was needed.

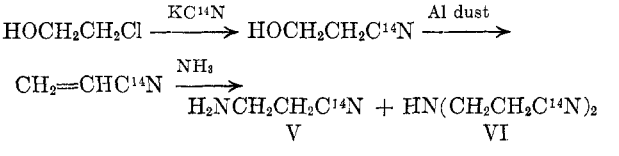
BAPN containing N^{15} in the amino group was obtained by reacting N^{15} phthalimide with acrylonitrile to produce β-phthalimidopropionitrile, which was then cleaved with hydrazine.[7] The preparation of BAPN containing C^{14} in the nitrile group (V) was first attempted *via* the following route:

Unexpected difficulty was encountered in the replacement of the bromine atom of III with cyanide. Only traces of the desired product, IV, could be isolated from the reaction mixture. Variations in the reaction conditions were studied, and the chloro and iodo analogs of III were prepared and tried, but the only product obtained was the hydroxy compound II. Since hydrolysis of the halogen appeared to be the main reaction, a nonaqueous solvent, N,N-dimethylformamide, was tried and did



give a small amount of IV. However, the yield was too low to be desirable for use with C^{14} materials.

Two other possible routes to V were rather cursorily attempted without success. Bubbling gaseous hydrogen cyanide slowly through ethylene imine, evaporating the excess reagents, and adding ethanolic hydrochloric acid gave only an uncrystallizable gum. No catalysts were tried. As far as the authors are aware this direct and obvious approach to BAPN has not been investigated. Reaction of β-chloroethylamine hydrochloride with inorganic cyanide likewise yielded only polymeric material. The desired compound was eventually obtained as follows:



Although the yields were still not high, this method had the advantage of simultaneously producing the labeled bis compound, VI, which was also desired for metabolic studies.

EXPERIMENTAL

β-Aminopropionitrile-amino-N^{15}. Potassium N^{15} phthalimide (Eastman) containing 34% N^{15} was dissolved in water and treated with hydrochloric acid. The free phthalimide was filtered off and thoroughly dried. A mixture of 9.6 g. of this product and 33 ml. of acrylonitrile was refluxed for 10 min. on a steam bath, then 1.0 ml. of a 40% solution of benzyltrimethylammonium hydroxide (Triton B) in methanol was gradually introduced beneath the surface of the refluxing liquid over a period of 15 min. The solution was introduced through a capillary and was forced into the reaction mixture under mild air pressure. Removal of excess acrylonitrile from the resulting clear yellow solution by distillation under reduced pressure left an essentially quantitative yield of β-phthalimidopropionitrile (IV) as a mass of granular yellow crystals. A small portion was decolorized with charcoal in boiling 70% ethanol solution and then crystallized from this solvent to yield colorless crystals, m.p. 151–152°, unchanged after four recrystallizations. Galat[8] reports m.p. 154–155.5°.

To effect hydrazinolysis, 11.7 g. of the crude yellow product, 1.9 g. of anhydrous hydrazine, and 42 ml. of 95% etha-

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