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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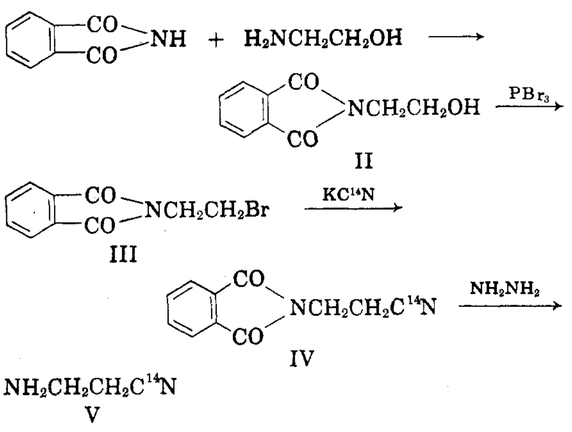
Following the demonstration that β-(N-γ-L-glutamyl)aminopropionitrile (I) is the natural causative agent of the skeletal deformities produced in rats by *Lathyrus odoratus* seeds,[3] it was readily established that the toxicity was due to the β-aminopropionitrile (BAPN) portion of the molecule.[4–6] 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:

$$\mathrm{HOCH_2CH_2Cl} \xrightarrow{\mathrm{KC^{14}N}} \mathrm{HOCH_2CH_2C^{14}N} \xrightarrow{\text{Al dust}}$$

$$\mathrm{CH_2{=}CHC^{14}N} \xrightarrow{\mathrm{NH_3}} \underset{\mathrm{V}}{\mathrm{H_2NCH_2CH_2C^{14}N}} + \underset{\mathrm{VI}}{\mathrm{HN(CH_2CH_2C^{14}N)_2}}$$

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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nol were mixed, warmed to 50° for 10 min., allowed to stand 1 hr. at room temperature, and then reheated to 60°, and concentrated hydrochloric acid was added with stirring until the *p*H dropped to 1. The mixture was stirred and heated at 60° for 2 hr. longer and then cooled in an ice bath. The precipitated phthalhydrazide was filtered off and the filtrate was adjusted to pH 10 with saturated aqueous sodium hydroxide solution. The basic solution was mixed with 2 g. of sodium chloride and extracted with ether for 5 hr. in a continuous extractor, and the extract was dried over anhydrous potassium carbonate. Concentration of the extract to a small volume and addition of 5% ethanolic hydrochloric acid caused the precipitation of 2.54 g. (41%) of BAPN hydrochloride, m.p. 165–166°. The m.p. of this salt has been reported to be 164°.[9] Analysis with the mass spectrometer showed 15.4 atom per cent N$^{15}$ excess in this product.[10]

*β-Aminopropionitrile-1-C.*$^{14}$ C$^{14}$ Barium carbonate was converted to C$^{14}$ potassium cyanide by the method of McCarter.[11] Yields varied from 82 to 84%.

A mixture of the radioactive potassium cyanide from 100 mg. of barium carbonate (specific activity 1 mc. per millimole), 14.8 g. of nonradioactive potassium cyanide, and 19.5 g. of ethylene chlorohydrin was stirred continuously at 55° and 6.5 ml. of water was added dropwise during a period of 1.75 hours.[12] Stirring was continued while the mixture was maintained at 55° for 45 min. after addition of the water was complete and then at 60° for 3 hr. longer. The reaction mixture was then extracted five times with 15-ml. portions of acetone, and the extract was fractionally distilled. Ethylene cyanohydrin distilled as a colorless liquid, 7.48 g. (44%), b.p. 223–224°.

The above product and 0.75 g. of aluminum dust were placed in a 50-ml. conical flask fitted with a reflux condenser and with a second condenser arranged for downward distillation.[12] Steam was passed through the reflux condenser and the flask was heated in an oil bath at 180° until distillation ceased (*ca.* 3 hr.). The distillate was collected in a centrifuge tube chilled in dry ice. The oil bath temperature was then raised to 280° and held there until dehydration was complete (total heating time 8 hr.). Decantation of the upper oily layer in the receiver from the lower frozen water layer gave 4.4 g. (79%) of radioactive acrylonitrile.

This material without further purification was placed in a sealed tube with 16 ml. of concentrated ammonium hydroxide and shaken for a few minutes until a homogeneous solution was formed. After 20 hr. at room temperature the contents of the tube were distilled to yield 1.40 g. (24%) of V, b.p. 69–70° (8 mm.), plus 2.28 g. (45%) of the bis compound, VI, b.p. 180–192° (8–10 mm.).[13] Each was converted to the hydrochloride with ethanolic hydrogen chloride in quantitative yield. The salt of V consisted of glistening white platelets, m.p. 165–166°, while that from VI appeared as fine white needles, m.p. 149–150°. These m.p. values have been reported as 164° and 148°, respectively.[9] The specific activity of the hydrochloride of V was 0.46 μc. per mg., and of that from VI was 0.48 μc. per mg.

*Reaction of N-(β-haloethyl)phthalimides with sodium or potassium cyanide.* In a typical experiment 8 g. of N-(β-bromoethyl)-phthalimide, (III),[14] 2.6 g. of potassium cyanide, and 140 ml. of 80% ethanol were continuously stirred and refluxed for 24 hr. The clear red-brown solution was concentrated to dryness at reduced pressure and the residue was extracted with boiling dioxane. The residue from evaporation of the dioxane extract was crystallized from water to give 2.6 g. of large plates, m.p. 125–126°. A recrystallized sample, m.p. 127–129°, proved to be identical with N-(β-hydroxyethyl)phthalimide, (II).[14] No other definite product could be isolated.

A repetition of this experiment using N,N-dimethylformamide as the solvent in place of 80% ethanol gave an 11% yield of impure N-(β-cyanoethyl)phthalimide, (IV), m.p. 139–144°, (pure IV melts at 151–152°). Extending the reaction time to 70 hr. at 120–130° gave no better results. When the procedure of Sakami *et al*[15] involving the use of acetone-free methanol as solvent was tried, unchanged III was recovered. When N-(β-chloroethyl)phthalimide[16] was refluxed with sodium cyanide in 50% ethanol, the mixture darkened rapidly and no definite product could be isolated. Reaction of N-(β-iodoethyl)phthalimide[17] with potassium cyanide in 95% ethanol gave II as the only product.

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## Anomalous Hofmann Elimination Reactions

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Weinstock[1] questions the conclusion of Ingold and Rogers[2] and in particular suggests that the alleged new *cis-trans* isomer, m.p. 107–8°, of the previously described α-benzylcrotonic acid (m.p. 99°) which these authors describe, is, in fact, 1-benzylcyclopropanecarboxylic acid. Such a possibility was considered by Rogers[3] and rejected for two reasons: the absorption of more hydrogen (3.25 atoms) on catalytic reduction in aqueous solution over Adam's platinum oxide catalyst than was required for full hydrogenation of the benzene ring system; and the isolation,[2] following ozonolysis in chloroform at 0° for 2 hr., of acetaldehyde as its 2,4-dinitrophenylhydrazone, m.p. 154°, raised on admixture with authentic material of m.p. 163°, and depressed by mixture with the dinitrophenylhydrazone of formaldehyde.

Small samples of both isomers being available, it has been possible to decide the point in the light of modern spectroscopic knowledge. The infrared absorption of the alleged isomer m.p. 107° not only differs greatly from that of the isomer m.p. 99°, but shows the peak at 9.70 μ, already recorded for 1-benzylcyclopropanecarboxylic acid by Piehl and Brown,[4] which Slabey[5] has shown to be charac-

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