lized to determine the insulin activity of the filtered extracts. A standard curve was prepared with dilutions of USP insulin reference standard. Triplicate samples of the extraction aliquots were then assayed, and data were converted to original units of insulin per unit weight of pancreas glands.

RESULTS AND DISCUSSION

Irradiation of the beef pancreas glands at doses between 10,000 and 20,000 rads produced significant increases in insulin yield when compared to the control sample (Table I). Beginning at 12,000 rads, an increase in yield occurs. The maximum yield obtained was an increase of 34.2% over the control with a dose of 20,000 rads.

From the data in Table I, it appears that 20,000 rads is the most effective dose of ^{60}Co γ-radiation for increasing insulin yields. Although it remains to be proven that it is a specific enzyme inactivation that results in the increased yield, this effect of γ-irradiation can be hypothesized. It is also possible that the irradiation could affect the insulin molecule. However, experiments conducted in this laboratory using reference standards in simulated gland concentrations have shown no significant loss in insulin as a result of γ-irradiation in these dose ranges. The insulin molecule, a small protein of molecular weight of approximately 6000, is much smaller than most enzymes. In addition, enzymes usually have unique subgroups attached to them which make them more susceptible to the effects of ionizing radiation (4).

The radioimmunoassay method used in this experiment does not assure the safety of these insulin extracts in humans. Further biological testing is necessary to allow clinical application. However, considering the present factors of increased population and increased utilization of insulin, in lieu of oral hypoglycemic agents with reported side effects, utilization of γ-radiation to increase the insulin yield of pancreas glands may be a means of increasing this insulin supply.

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ˣ To whom inquiries should be directed.

New Compounds: Monoesters of α-Aminobenzylphosphonic Acid

W. FRANKLIN GILMOREˣ and HILMER A. McBRIDE

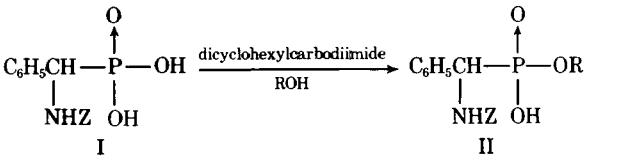
Abstract □ The reaction of α-(*N*-carbobenzoxyamino)benzylphosphonic acid with *n*-propanol or ethanol in the presence of triethylamine and dicyclohexylcarbodiimide gave the title compounds in good yields.

Keyphrases □ α-Aminobenzylphosphonic acid monoesters—synthesis □ Phosphonic acid monoesters, α-aminobenzyl—synthesis

While investigating methods of incorporating α-aminophosphonic acids into peptides, the conversion of aminophosphonic acids to monoesters became of interest. It is well known that phosphonic acids can be converted to monochlorides by use of 1 equivalent of phosphorus pentachloride. Addition of the monochlorides to alcohols furnishes the monoesters (1). While this method is satisfactory, it is laborious. Monoalkyl esters of *N*-substituted α-aminophosphonic acids may be prepared by treating a Schiff base with an alkaline salt of an alkyl dihydrogen phosphonate (2). This method is not satisfactory for preparing the monoesters of α-(*N*-carbobenzoxyamino)phosphonic acids. Partial hydrolysis of the diesters of aminophosphonic acids has been used as a source of the monoesters (3).

Dicyclohexylcarbodiimide has been used for the synthesis of esters of phosphorus acids (4–8). The preparation of monoesters from α-(*N*-carbobenzoxyamino)benzylphosphonic acid (I) by treatment with alcohols and dicyclohexylcarbodiimide is the subject of this report. Scheme I illustrates this synthesis.

The α-(*N*-carbobenzoxyamino)benzylphosphonates (II) can be converted to the deblocked amine hydrobromides by treatment with hydrogen bromide in acetic acid. The water-soluble hydrobromide salts can be converted to the amino esters by use of silver oxide.



I

Z = carbobenzoxy

II

R = ethyl or propyl

Scheme I

EXPERIMENTAL[1]

***n*-Propyl-α-aminobenzylphosphonate**—A solution of 6.4 g (20 mmoles) of I (9), 4.21 g (20 mmoles) of dicyclohexylcarbodiimide, and 2.5 g (25 mmoles) of triethylamine in 100 ml of *n*-propanol was stirred for 16 hr at 25° and the dicyclohexylurea was removed by filtration. Evaporation of the *n*-propanol, partitioning of the residue between methylene chloride and 1 *N* HCl, and evaporation of the dried methylene chloride gave 7.9 g of a solid. Recrystallization of this solid from acetone afforded 5.5 g (76%) of the propyl ester, mp 181–182°; IR (KBr): 3300 (N—H), 1725 (C=O), and 1250 (P—O) cm^{-1}; NMR (d_6-dimethyl sulfoxide): δ 0.89 (t, 3, CH_3), 1.50 (m, 2, CH_3CH_2), 3.82 (m, 2, $CH_3CH_2CH_2O$), 5.12 (s, 2, $CH_2C_6H_5$), and 7.65 (s, 10, aromatic).

Anal.—Calc. for $C_{18}H_{22}NO_5P$: C, 59.50; H, 6.10; N, 3.86; P, 8.52. Found: C, 59.46; H, 6.17; N, 3.83; P, 8.12.

The ethyl ester, mp 188–190° [lit. (3) mp 183–189°], was obtained in a similar manner.

Anal.—Calc. for $C_{17}H_{20}NO_5P$: C, 58.45; H, 5.77; N, 4.01; P, 8.86. Found: C, 58.70; H, 5.81; N, 3.93; P, 8.69.

Propyl-α-aminobenzylphosphonate Hydrobromide—To a suspension of 3.6 g (10 mmoles) of the propyl ester II in 30 ml of acetic acid was added 10 g (5.5 mmoles/g) of 45% HBr in acetic acid. The suspension was stirred for 40 min, after which all of the ester had dissolved. The solution was diluted with dry ether to precipitate the hydrobromide, which was collected by filtration and recrystallized three times from methanol–ether to yield 2.5 g (81%) of the hydrobromide, mp 156–158°; IR (KBr): 1210 (P—O) cm^{-1}, no carbonyl absorption; NMR (D_2O): δ 0.85 (t, 3, CH_3), 1.60 (m, 2, CH_3CH_2), 3.83 (m, 2, $CH_3CH_2CH_2O$), 4.65 (d, 1, J = 16 Hz, CH—P), and 7.62 (s, 5, phenyl); mass spectrum (70 ev): *m/e* (relative intensity) 124(6), 122(10), 81(9), 79(10), 43(100), and 41(30).

Anal.—Calc. for $C_{10}H_{17}BrNO_3P$: C, 38.73; H, 5.53; N, 4.52; P, 9.99. Found: C, 39.20; H, 4.94; N, 4.55; P, 9.96.

[1] Melting points were determined with a Thomas-Hoover Unimelt melting-point apparatus and are corrected. NMR spectra were taken on a Jeolco model C-60-HL spectrometer using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as the internal standard. IR spectra were taken on either a Perkin-Elmer model 137 or 256 spectrophotometer. Mass spectra were taken by Dr. John K. Baker using a DuPont CEC model 21-492 spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

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[x] To whom inquiries should be directed.

COMMUNICATIONS

Interaction of Salicylic Acid with Adenosine and Adenosine Triphosphate: Potential Mechanism of Intensifying Aspirin-Induced GI Blood Loss

Keyphrases □ Salicylic acid—interaction with adenosine and adenosine triphosphate, related to mechanism of intensifying aspirin-induced GI blood loss □ Adenosine and adenosine triphosphate—interaction with salicylic acid, mechanism of aspirin-induced GI blood loss □ Aspirin—salicylic acid-adenosine interaction, possible mechanism of intensifying aspirin-induced GI blood loss

To the Editor:

Several studies (1–4) indicated that aspirin-induced gastric or GI bleeding is usually a local effect resulting from contact of aspirin particles, or saturated solutions of aspirin surrounding these particles, with the mucosa. Maudlin (5) also stated that bleeding and ulceration are due to a local focal necrosis. However, Woznicki and Mrtek (6) expressed the opinion that the mechanism of aspirin-induced GI blood loss is due to a combination of both local and systemic effects. They explained the systemic effect by the role of aspirin in reducing platelet aggregation through elimination of the second wave of platelet aggregation induced by adenosine diphosphate. These authors defended their opinion by the fact that aspirin is being used experimentally to prevent formation of thromboemboli. However, no work has been published to support this theory.

Preliminary investigations in our laboratories have indicated interaction between salicylic acid and adenosine or adenosine triphosphate. The presence of the phosphate moiety does not appear to be critical for the complexation. The complexes formed also