sodium sulfate. Removal of the solvent under reduced pressure gave a residue which crystallized on cooling. Two recrystallizations from aqueous methanol gave colorless material (180 mg.) melting at 159–160.5°; [α] + 170°; λ_{max} 241 mμ (log ε = 4.20) (reported[14]: m.p. 166–168°; $[\alpha]_D$ +175.9°). The melting point of a sample mixed with authentic 11α-hydroxyprogesterone was 161–169°. The infrared absorption spectrum (KBr disk) of this compound was significantly different from that of 11α-hydroxyprogesterone which had been recrystallized from aqueous acetone.

The chromous chloride reduction product was oxidized with chromic anhydride in pyridine[15] to give 11-oxoprogesterone, m.p. 173.5–177.0; $[\alpha]_D$ +238° (acetone); reported[16]: m.p. 172–174°; $[\alpha]_D$ +238.5 ± 8° (acetone).

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[CONTRIBUTION FROM THE GUY AND BERTHA IRELAND RESEARCH LABORATORY, DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF NORTH DAKOTA SCHOOL OF MEDICINE]

Standard Method for Synthesis of Some 1-C^{14}-Labeled Amino Acids[1]

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A standard, 5-step method for the synthesis of 1-C^{14}-labeled glycine, DL-alanine, and DL-leucine has been investigated. The procedure may be of practical value for the preparation of carboxyl-labeled amino acids. The technique is limited to amino acids which form phthaloyl derivatives.

It has been reported that 1-C^{14}-labeled fatty acids can be prepared by decarboxylating the silver salt of the acid with a halogen to the corresponding alkylhalide, and subsequently reversing the process with $C^{14}O_2$ in the Grignard reaction.[3]

We felt that the carboxyl-labeled amino acids could be prepared in an analogous fashion; however, the silver salts of the α-amino acids when decarboxylated with a halogen produce the corresponding alkylidenimine hydrohalides rather than the α-aminoalkylhalides.[4] It was thought that the alkylidenimine compounds may have arisen through dehydrohalogenation of the α-amino alkylhalides. Blocking of the amino group would preclude this dehydrohalogenation, and might thus permit the synthesis of 1-C^{14}-labeled amino acids *via* nitrilation with NaC^{14}N and subsequent hydrolysis. This supposition was substantiated using phthalic anhydride as the blocking agent for the amino group.

Three amino acids have been prepared according to the procedure outlined in relatively good yield. These are 1-C^{14}-labeled glycine, DL-alanine, and DL-leucine.

EXPERIMENTAL

The experimental technique is identical in the case of all three amino acids, and the synthesis of glycine-1-C^{14} will be presented as an example of the method.

Phthaloylglycine. The phthaloyl derivatives of the amino acids were prepared according to the suggestion of Billman and Harting[5] A mixture of finely ground glycine[6] and a 10% excess of phthalic anhydride were fused on an oil bath for 15 min. at 185°. The liquid product, which solidified when cooled, was recrystallized twice from 10% ethanol.

Silver phthaloylglycinate. Five g. of finely powdered phthaloylglycine was suspended in 100 ml. of 10% ethanol and the pH adjusted to 6.5 with 6*N* NaOH. A 25% excess of aqueous silver nitrate was slowly added to the solution with stirring. The white precipitate, silver phthaloylglycinate, was allowed to stand in the dark for 1 hr. It was then filtered under suction. The silver salt was washed three times with water and then twice with acetone-free absolute methanol. Yield: 80–85%.

N-bromomethylphthalimide. The success of the decarboxylation demands that all glassware and reagents be scrupulously dry. The moist silver salt was placed in an oven at 65°. until hard and then powdered. Five g. of the salt was added to a flask fitted with a ground glass joint. The flask was then placed into a borosilicate glass vacuum desiccator containing P_2O_5. The desiccator was evacuated to a pressure of 1 mm. and placed in an oven at 65°. The temperature was slowly increased to 90° over a 2 hr. period. The desiccator was re-evacuated every 4 hr. Drying was continued for a total of 72 hr.

One hundred ml. of anhydrous CCl_4 (distilled and then dried over P_2O_5 for 3 days) was added to the silver phthaloylglycinate and the suspension heated to the boiling point of the solvent on a hot plate. The mixture was allowed to cool for 1 min. at room temperature, and 1.5 equivalents of dry Br_2 (shaken twice with concentrated H_2SO_4) in 5 ml. of anhydrous CCl_4, were added rapidly with shaking. The vigorous evolution of CO_2 was observed immediately. The suspension was shaken for an additional 5 min. and then refluxed gently for 1 hr. The solvent was removed at room

(1) A preliminary report of this investigation has been published.[2] The study was supported in part by a grant from the North Dakota Cancer Society.

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(6) A DL mixture of alanine and leucine was employed in the synthesis of their phthaloyl derivatives.

temperature *in vacuo*, and 35 ml. of a mixture of acetone-free methanol and dioxane (5:2) was added to the residue which contained the *N*-bromomethylphthalimide and some phthaloylglycine. The solution was warmed and then filtered to remove the silver bromide. The pH of the filtrate was adjusted to 6.5 with a saturated solution of NaOH in acetone-free absolute methanol. No attempt was made to isolate the *N*-bromomethylphthalimide.

Labeled N-cyanomethylphthalimide. The labeled nitrile was prepared according to the method of Sakami, *et al.*[7] Sodium cyanide-C^{14}, in 2 ml. of acetone-free absolute methanol, was added to the solution containing the *N*-bromomethylphthalimide. The mixture was shaken and allowed to stand for 6 hr. The nitrile was not isolated.

1-C^{14}-labeled glycine. The solvents containing the labeled *N*-cyanomethylphthalimide were removed *in vacuo* and an acid mixture (22 ml. glacial acetic, 50 ml. 20% HCl) was added to the residue and refluxed for 15 hr. The hydrolysate was cooled in the refrigerator and the insoluble phthalic acid removed by filtration. The filtrate was taken to dryness *in vacuo* at 100° and 25 ml. of concentrated HCl was added. The insoluble sodium chloride was removed and the solution again taken to dryness at 100° *in vacuo*. This procedure was repeated. The residue was finally taken up in a minimal amount of boiling water and 5 volumes of 95% ethanol were added, followed by a small amount of pyridine. The solution was cooled overnight in the refrigerator. The glycine-1-C^{14} was recrystallized twice from an alcohol-water mixture.

Amino acid assay. After recrystallization, the 1-C^{14}-labeled amino acids were chromatographed on paper, located with 0.05% ninhydrin in 1-butanol, and eluted. The activities of the isolated compounds, corrected for self-absorption, were determined in a Tracerlab gas flow counter. The total amount of amino acid was measured by quantitative paper chromatography.[8] Finally, derivatives of the amino acids were prepared and assayed for radioactivity. Within experimental error these derivatives were found to be as radioactive as their amino acid precursors. The results are summarized in Table I.

TABLE I
SYNTHESIS OF 1-C^{14} LABELED AMINO ACIDS

Amino Acid	% Radioactive Yield[a]	Specific Activity $\times 10^4$ counts/minute/mM[b]	Derivative
DL-Alanine	41.3	4.8	Phthaloyl
Glycine	57.5	6.3	Phthaloyl, picrate
DL-Leucine	37.6	2.7	Picrolonate

[a] Calculated on the basis of NaCN-C^{14} used (Activity—2×10^6 counts/minute). [b] Specific activity 39 counts/minute/mM for NaCN-C^{14}.

DISCUSSION

The decreased specific activities of the 1-C^{14} amino acids relative to NaCN-C^{14}, in the presence of the higher yield data, suggest the decarboxylation of the silver phthaloyl derivatives is not stoichiometric. Similar findings were reported for organic acids.[9]

While the data presented in Table I suggest that the procedure may be of practical value, the method is limited to those amino acids which form phthaloyl derivatives. It has been reported that tyrosine, tryptophan, taurine, and serine do not form such derivatives, and thus the procedure would not be applicable to these amino acids.[5] Furthermore, phenylalanine might be expected to undergo bromination in the course of the silver salt decarboxylation step.

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GRAND FORKS, N. D.

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[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

1-[(2-Dialkylaminoethoxy)phenyl]-2-amino-1-propanols

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2-And 4-(2-dimethylaminoethoxy)phenyl- and 2- and 4-(2-diethylaminoethoxy)phenyl-2-amino-1-propanol were synthesized. Derivatives of these compounds, wherein the primary amino group was variously substituted, were also prepared.

An investigation was undertaken with the object of preparing compounds of the phenethylamine type, having a dialkylaminoalkoxy substituent in the phenyl ring. It was hoped that thereby compounds of pharmacological interest might be attained.

Hundreds of phenethylamine derivatives have been prepared for pharmacological testing. Variations in structure have produced compounds with different sympathomimetic properties of clinical interest. Thus, there have been found among these compounds drugs which act as vasoconstrictors, bronchodilators, central nervous system stimulants, analgetics, and uterine contractors.[1] The relationship between activity and structure has been

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