mixture of this substance and the one obtained from 4-nitroguaiacol melted at 96–97°.

Summary

It has been shown that the mercuration of 5-nitroguaiacol results principally in the formation of 6-acetoxymercuri-5-nitroguaiacol and 4,6-diacetoxymercuri-5-nitroguaiacol.

In the course of the work three new compounds, 6-bromo-5-nitroguaiacol, 4,6-dibromo-5-nitroguaiacol and 4,6-dibromoguaiacol, have been prepared and characterized.

Evidence has been offered that the substance mercurated was in fact 5-nitroguaiacol and not an isomer.

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Amino Acid Intermediates: α-Amino-γ-lactones

BY JEANNE FILLMAN AND NOEL ALBERTSON

α-Amino-γ-lactones have been used not only for the synthesis of γ-hydroxyamino acids, but also for the preparation of such amino acids as methionine[1] and canaline.[2] In general, the lactones have been prepared by the reaction of the appropriate oxide with a malonic or acetoacetic ester. For example, γ-hydroxyproline has been synthesized from epichlorohydrin and malonic ester[3] and γ-hydroxyleucine (V) recently was synthesized from isobutylene oxide and actamidomalonic ester.[4] In the latter instance the condensation product was an oil so that hydrolysis gave glycine as an impurity difficult to remove.

Since lactones may also be prepared from β,γ- and γ,δ-unsaturated acids,[5] a possible route to γ-hydroxyamino acids would involve condensation of an allyl halide with an acylaminomalonic or acylaminocyanoacetic ester and conversion to the amino acid via the lactone.

yield[7] of recrystallized product (I and II, respectively). Hydrolysis of I with hydrochloric acid for four hours gave an 85% yield of γ-hydroxyleucine lactone hydrochloride (IV). The same lactone was obtained on acid hydrolysis of the cyano intermediate (II) or methylallylglycine (III), the latter amino acid being obtained from I or II by basic hydrolysis.[7] Conversion of the lactone to γ-hydroxyleucine was accomplished by means of the flavianate according to the procedure of Dakin.[4]

This method of synthesizing γ-hydroxyleucine is simpler experimentally and gives better yields and a purer[8] product than the method using isobutylene oxide.

One would normally expect a γ-hydroxy acid to form a lactone, but Dakin points out that γ-hydroxyleucine does not readily give a lactone on boiling with hydrochloric acid. This is in marked contrast to the phenyl isocyanate derivative which has been obtained only in the form of the lactone. However, it has been found that under proper conditions (refluxing for five and one-half hours with concentrated hydrochloric acid) γ-hydroxyleucine is converted to the lactone hydrochloride as shown by mixed melting point and chlorine analysis. At the end of three and one-half hours the conversion was not yet complete, so that lactonization of this hydroxy acid requires relatively strenuous treatment. This is especially surprising in view of the structure of γ-hydroxyleucine. Since "substituent alkyl groups decidedly
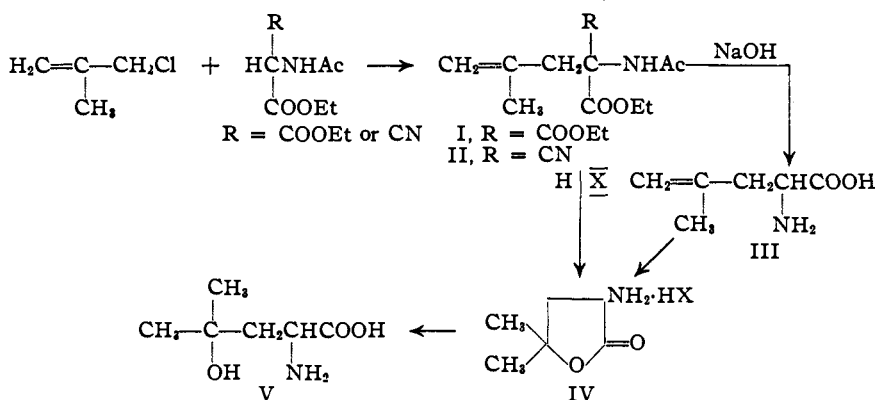
Methylallyl chloride has been reported to condense with acetamidomalonic ester in 79% yield[6] and with acetamidocyanoacetic ester in 82%

(1) (a) Hill and Robson, Biochem. J., 30, 246 (1936); (b) Livak, Britton, Van der Weele and Murray, THIS JOURNAL, 67, 2218 (1945).

(2) Kitagawa, J. Agr. Chem. Soc. Japan, 12, 871 (1936); C. A., 31, 1362 (1937).

(3) Leuchs, Ber., 38, 1937 (1905).

(4) Dakin, J. Biol. Chem., 154, 549 (1944).

(5) Fittig, Ann., 208, 94 (1881); 283, 47, 269 (1894); Ber., 27, 2658 (1894).

(6) Albertson and Archer, THIS JOURNAL, 67, 308 (1945).
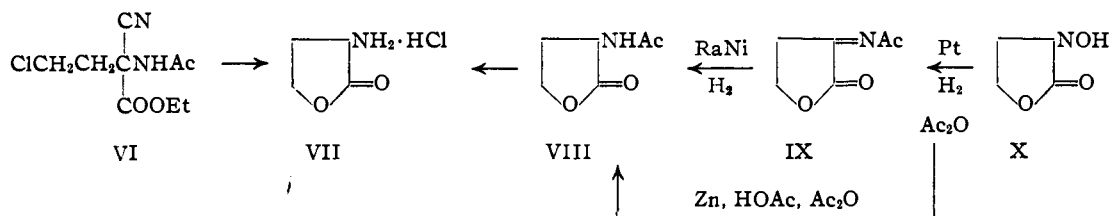
(7) Albertson, ibid., 68, 450 (1946).

(8) Apparently the product prepared by Dakin (ref. 4) still contained a trace of glycine since it gave a phenyl isocyanate derivative melting at 188–189° with slight previous softening. We found that this derivative melted at 200–201°. The lactone (IV) gave a phosphotungstate, a copper salt, a Reinecke salt and a flavianate in agreement with the derivatives reported by Dakin.

favor the formation of lactones[9]" one might have anticipated an almost spontaneous lactonization. In contrast to the hydroxyamino acid (V) the unsaturated acid (III) is readily converted to the lactone by hydrochloric acid.

Inasmuch as Sorensen has prepared allylglycine in high yields by hydrolyzing allyl o-carboxybenzamidomalonic acid with concentrated hydrochloric acid,[10] it is apparent that allylglycine is not converted to the lactone under these conditions. It has been found, however, that either hydrobromic or hydriodic acid will convert allylacetamidocyanoacetic ester to the lactone, whereas the use of hydrochloric acid results in the formation of allylglycine. The lactone was converted to the benzoyl derivative and one dl-form was isolated.

In an attempt to extend this method of synthesis to γ-hydroxyproline the commercially available 1,3-dichloropropene was condensed with acetamidocyanoacetic ester and the product hydrolyzed with hydrochloric acid to give ω-chloro allylglycine. "Lactonization" of this amino acid should give the known α-amino-δ-chloro-γ-valerolactone from which γ-hydroxyproline has previously been prepared.[11] However, no lactone could be obtained by treatment of ω-chloroallylglycine with hydrobromic, hydriodic, sulfuric, perchloric or periodic acids or with hydrogen chloride in acetic acid, probably because of steric effects.

Inasmuch as γ-halogen substituted acids are also useful in the preparation of lactones an alternative synthesis of α-amino-γ-lactones would involve the preparation and hydrolysis of a γ-halogen substituted acetamidocyanoacetic ester. It was found that hydrochloric acid readily converted β-chloroethylacetamidocyanoacetic ester, VI, to the known α-amino-γ-butyrolactone hydrochloride, VII, an intermediate in the synthesis of methionine[1] and canaline.[2]

halide to form a vinyl halide which would escape from the condenser.

It is interesting to note that Painter[13] attempted to prepare β- and γ-halogen amino acids by hydrolysis of appropriately halogen substituted benzamidomalonic esters but was unable to isolate the desired amino acids after hydrolysis. It is very likely that, at least in the case of the γ-halogen acids, lactones were formed on hydrolysis.

An attempt to react VI with potassium benzohydroxamate with a view to synthesizing canaline was unsuccessful. Replacement of the chlorine by iodine still gave negative results.

An alternative synthesis of α-amino-γ-butyrolactone hydrochloride involved reductive acetylation of the readily available α-oximino-γ-butyrolactone followed by hydrolysis of the intermediate α-acetamido-γ-butyrolactone, VIII.[14] Although zinc dust reduced the oxime to the acetamido compound, catalytic reduction with a platinum catalyst in acetic anhydride solution resulted in the uptake of only one mole of hydrogen to give α-acetimido-γ-butyrolactone, IX. With a Raney nickel catalyst, IX was rapidly and quantitatively reduced to the acetamido compound VIII. Upon hydrolysis this gave α-amino-γ-butyrolactone hydrochloride identical with that previously prepared. Hydrolysis of the intermediate α-acetimido-γ-butyrolactone gave ammonium chloride as the only crystalline product.

Experimental

γ-Hydroxyleucine Lactone Hydrochloride (IV).—Seventy-one and six-tenths grams of diethyl methylallylacetamidomalonate[6] was refluxed for four hours with 250 ml. of concentrated hydrochloric acid. The resulting solution was concentrated in vacuo and the residue taken up in hot ethanol. Upon cooling and filtering there was obtained 28.8 g. of product. By concentrating the filtrate and cooling an additional 8.3 g. was obtained, m. p. 207–209°. The yield was 85%. An analytical sample, recrystallized from ethanol, melted at 208–209°.

VI　　　　　　　VII　　　　　　　VIII　　　　　　　IX　　　　　　　X

Zn, HOAc, Ac₂O

The β-chloroethylacetamidocyanoacetic ester was synthesized from ethylene chlorobromide and sodioacetamidocyanoacetic ester in toluene. Previous attempts to condense ethylene chloride or ethylene bromide with acylaminomalonic esters have been unsuccessful.[12] However, these attempted syntheses were carried out in alcohol in which case the sodium ethylate was undoubtedly basic enough to remove HX from the ethylene

Anal. Calcd. for C₆H₁₁NO₂·HCl: C, 43.51; H, 7.31; N, 8.46; Cl, 21.41. Found: C, 43.50; H, 7.20; N, 8.26; Cl, 21.49.

When methylallylacetamidocyanoacetic ester (II)[7] or methylallylglycine (III)[7] was used in the above experiment the same lactone was obtained.

The benzoyl derivative, recrystallized from aqueous methanol, melted at 176°.

Anal. Calcd. for C₁₃H₁₅NO₃: N, 6.01. Found: N, 6.01.

The carbobenzoxy derivative, recrystallized from aqueous ethanol, melted at 91–93°.

(9) Schmidt, "A Textbook of Organic Chemistry," 2nd English ed., D. Van Nostrand Co., Inc., New York, N. Y., 1932, p. 230.

(10) Sorensen, *Ber.*, 41, 3388 (1908).

(11) McIlwain and Richardson, *Biochem. J.*, 33, 45 (1939).

(12) Dunn and Smart, *J. Biol. Chem.*, 89, 41 (1930).

(13) Painter, THIS JOURNAL, 62, 232 (1940).

(14) This compound has been prepared by reductive acetylation of α-keto-γ-butyrolactone phenylhydrazone using Raney nickel catalyst: Snyder, Andreen, Cannon and Peters, *ibid.*, 64, 2082 (1942).

Anal. Calcd. for $C_{14}H_{17}NO_4$: N, 5.32. Found: N, 5.32.

The phenyl isocyanate derivative, recrystallized from aqueous methanol, melted at 200–201°.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.86; H, 6.41; N, 11.30.

The lactone gave a flavianate which decomposed at 273–276°.

γ-**Hydroxyleucine (V).**—Twenty-eight grams of γ-hydroxyleucine lactone hydrochloride (IV) was converted to γ-hydroxyleucine by use of flavianic acid according to the procedure of Dakin.[4] There was obtained 20.6 g. of amino acid melting at 220–222° when dried at 65°.

Anal. Calcd. for $C_6H_{13}NO_3 \cdot H_2O$: N, 8.50. Found: N, 8.52.

When dried at 100° *in vacuo,* the amino acid lost water and melted at 230–232°.

Anal. Calcd. for $C_6H_{13}NO_3$: N, 9.52. Found: N, 9.38.

The amino acid gave a flavianate, reineckate and phosphotungstate agreeing in properties with those reported by Dakin.[4]

Lactone from α-Hydroxyleucine.—Five grams of γ-hydroxyleucine was refluxed for five and one-half hours with 1:1 hydrochloric acid. The solution was concentrated *in vacuo* and the residue recrystallized from ethanol, m. p. 208–209°. It did not depress the melting point of γ-hydroxyleucine lactone hydrochloride.

Anal. Calcd. for $C_6H_3NO_3 \cdot HCl$: Cl, 193.1. Calcd. for $C_6H_{11}NO_2 \cdot HCl$: Cl, 21.49. Found: Cl, 21.30.

When γ-hydroxyleucine was refluxed with hydrochloric acid for only three and one-half hours the reaction mixture was a mixture of hydroxy amino acid and lactone.

Allylglycine.—Allylacetamidocyanoacetic ester was refluxed with hydrochloric acid (6 ml. of 1:1 aqueous acid per gram of ester) for five hours. The solution was charcoaled, filtered and concentrated *in vacuo.* The residue was taken up in water and made basic with sodium hydroxide to expel ammonia. The mixture was then made just acid with hydrochloric acid, cooled and filtered to give platelets melting at 170–190°. Three recrystallizations from water gave crystals, m. p. 212–215°.

Anal. Calcd. for $C_5H_9NO_2$: N, 12.17. Found: N, 12.08.

Benzoyl-*dl*-allylglycine.—Three grams of the above lactone was benzoylated in the usual manner. The product, twice recrystallized from water, melted at 105–106°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: N, 6.39. Found: N, 6.33. Bromine titration indicated 1.00 double bonds.

Benzamido-γ-hydroxynorvaline Lactone.—Hydrolysis of allylacetamidocyanoacetic ester was carried out as above with either hydrobromic or hydriodic acid. However, as soon as the ammonia had been expelled from the basic solution benzoyl chloride was added. The benzoyl derivative was isolated in the usual manner, freed of benzoic acid with Skellysolve B and recrystallized from small volumes of ethanol. The product was triturated with ether and finally recrystallized from water, m. p. 140–141°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: N, 6.39. Found: N, 6.41. It absorbed no bromine.

ω-**Chloroallylglycine.**—1,3-Dichloropropene[15] was condensed with acetamido-cyanoacetic ester and the resulting product hydrolyzed with hydrochloric acid according to methods previously described.[7] The yield of ω-chloroallylglycine, recrystallized from aqueous ethanol, was 38% m. p. 236°.

Anal. Calcd. for $C_5H_8ClNO_2$: N, 9.30. Found: N, 9.38.

The benzoyl derivative, recrystallized from aqueous ethanol, melted at 150–151°.

(15) A commercial sample obtained from Columbia Organic Chemicals Co., Inc., was used. Nearly all boiled at 104–106° at 761 mm., $n^{25}D$ 1.4651. It was therefore mainly the α form. *Cf.* Hatch and Moore, *ibid.,* **66,** 285 (1944).

Anal. Calcd. for $C_{12}H_{12}ClNO_3$: Cl, 13.97. Found: Cl, 13.68.

When chloroallylglycine was refluxed for four hours with hydrobromic, hydriodic, sulfuric, perchloric or periodic acid and the mixture then benzoylated only benzoyl-ω-chloroallylglycine was obtained. Hydrogen chloride in acetic acid gave only the amino acid hydrochloride.

β-**Chloroethylacetamidocyanoacetic Ester (VI).**—To a solution of 11.5 g. of sodium in 150 ml. of dry alcohol there was added 85 g. of ethyl acetamidomalonate. The alcohol was distilled off and toluene was dripped in simultaneously until no more alcohol remained. Then 338 g. of ethylene chlorobromide was added and the mixture refluxed twenty-nine hours. The precipitated sodium bromide (47 g.) was removed by filtration and the filtrate concentrated *in vacuo.* The residual oil (93.6 g.) was dissolved in alcohol and diluted with ice water. There was thus obtained 65 g. of crystalline product.

The product gave a precipitate when boiled with alcoholic silver nitrate and ammonia when boiled with sodium hydroxide. Probably a small amount of bromoethylacetamidocyanoacetic ester was also obtained in this reaction.

An analytical sample, recrystallized several times from ethyl acetate–Skellysolve B, melted at 109.5–111.5°.

Anal. Calcd. for $C_9H_{13}ClN_2O_3$: N, 12.04. Found: N, 11.46.

α-**Amino-γ-butyrolactone Hydrochloride from VI.**—When chloroethylacetamido-cyanoacetic ester was refluxed with concentrated hydrochloric acid for five hours, the solution concentrated to dryness, and the residue recrystallized several times from 95% alcohol the product was α-amino-γ-butyrolactone hydrochloride. The melting point was not depressed when mixed with a sample (m. p. 198–199.5°) obtained by the hydrolysis of 3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine.

α-**Acetimido-γ-butyrolactone (IX).**—Reduction of 11.5 g. of α-oximino-γ-butyrolactone[14] was effected in the presence of 0.3 g. of Adams platinum oxide catalyst, 28 ml. of acetic anhydride and 72 ml. of acetic acid at 50° and 50 lb. pressure. The residue, after removal of the solvent and catalyst, was washed well with water and recrystallized from methanol. The product, 7.0 g. of long needles, melted at 156°.

Anal. Calcd. for $C_6H_7NO_2$: N, 9.93. Found: N, 10.04.

Hydrolysis of this compound with hydrochloric acid gave ammonium chloride.

α-**Acetamido-γ-butyrolactone (VIII) from IX.**—A solution of 1.41 g. of α-acetimido-γ-butyrolactone was reduced in two minutes with a Raney nickel catalyst in ethanol. The product, after recrystallization from ethyl acetate, melted at 79–81°.[14] It did not depress the melting point of a sample prepared by reductive acetylation of (X) as described below. Hydrolysis of the product with hydrochloric acid gave α-amino-γ-butylactone hydrochloride.

α-**Acetamido-γ-butyrolactone (VIII) from X.**—A solution of 4.6 g. of oxime (X) in 100 ml. of acetic acid and 30 ml. of acetic anhydride was stirred during the addition of 12 g. of zinc dust portionwise. The mixture was filtered and the filtrate concentrated *in vacuo.* The residue was recrystallized from benzene–Skellysolve B and then ethyl acetate. Yield was 3.6 g. melting at 72–76°. Another recrystallization from ethyl acetate raised the melting point to 81–83°.

Summary

A synthetic approach to the synthesis of γ-hydroxyamino acids involving condensation of an allyl halide with an acylaminomalonic or acylaminocyanoacetic ester, hydrolysis to the lactone and conversion to the amino acid has been illustrated by the preparation of γ-hydroxyleucine.

The lactone of γ-hydroxynorvaline has also been synthesized by the same procedure, but the method failed to give the requisite α-amino-δ-chlo-

ro-γ-valerolactone required for the synthesis of γ-hydroxyproline.

The preparation of α-amino-γ-butyrolactone

by hydrolysis of β-chloroethylacetamidocyanoacetic ester is described.

Studies in the Indole Series. VIII. Yohimbine (Part 1). The Mechanism of Dehydrogenation of Yohimbine and Related Compounds[1]

BY PERCY L. JULIAN, ARTHUR MAGNANI, JOSEF PIKL[2] AND WILLIAM J. KARPEL

The work reported in this communication had its origin in attempts to synthesize the basic ring structure of yohimbine by a procedure presented schematically with formulas I → IV.

(Ia) R = H
(Ib) R = CH₃

(IIa) R = H
(IIb) R = CH₃

(IIIa) R = H
(IIIb) R = CH₃

(IVa) R = H
(IVb) R = CH₃
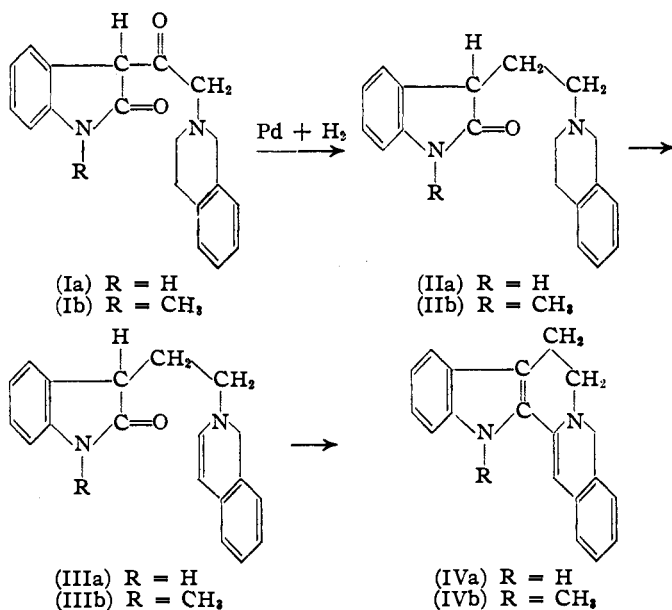
At the time this investigation began, which was more than a decade ago, the successful preparation of the desired 3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ia) from oxindole and ethyl N-tetrahydroisoquinolyl acetate,[3] as well as the reduction of Ia to 3-(2-N-tetrahydroisoquinolylethyl)-oxindole (IIa) could be predicted[4] and indeed was ultimately realized in practice. Sufficient information was also available then and later to indicate that, once compound IIIa were available, enolization of the hydrogen atom at position 3 of the oxindole nucleus could be used for ring closure. The crux of the whole synthesis, however, rested upon the ability to dehydrogenate IIa to IIIa, and this

in turn directed closer attention to the end-products from the dehydrogenation of yohimbine and indeed to the mechanism of this dehydrogenation.

When the synthesis of the yohimbine ring structure outlined above was projected the accepted formula for yobyrine, one of the principal dehydrogenation products of yohimbine, was IVa.[5] This structure, like IIIa, is that of a 1,2-dihydroisoquinoline and repeated efforts to prepare 1,2-dihydroisoquinolines hitherto have resulted in failure.[6] Only one case of such a preparation is reported in the literature, namely, that of Cooke and Gulland[7] who claim dehydrogenation of 2-methyltetrahydroisoquinoline to 2-methyl-1,2-dihydroisoquinoline with palladous chloride. Their evidence, however, is poor and subject to question. Our early failures to dehydrogenate IIb to 1-methyl-3-(2-N-dihydroisoquinolylethyl)-oxindole (IIIb) threw grave doubt upon the validity of IVa as representing the structure of yobyrine, despite the fact that the continuous conjugation in IVa might presumably favor the formation of a 1,2-dihydroisoquinoline in the case of the dehydrogenation of yohimbine to yobyrine. Moreover, Pruckner and Witkop[8] in the meantime proposed a new structure for yobyrine, involving a mechanism for the dehydrogenation of yohimbine more consistent with our experiences and those of others. Their results we have substantiated by a complete synthesis of yobrine.[9]

Both 1-methyl-3-(N-tetrahydroisoquinolylacetyl)-oxindole (Ib) and its unmethylated analog, (Ia), on catalytic reduction gave material whose empirical analyses correspond to substances IIb and IIa, respectively. There seems to be no fundamental difference in this case between reduction of the unmethylated and methylated acyl oxindoles such as Horner has indicated.[10]

(1) Presented in part as Indole Paper VIII before the Spring Meeting of the American Chemical Society at Boston, in April, 1939. For Paper IX in this series, see THIS JOURNAL, 67, 1203 (1945).

(2) Present address: Jackson Laboratory, du Pont Company, Wilmington, Delaware.

(3) Wedekind and Oechslen, Ber., 36, 1161 (1903).

(4) Julian, Pikl and Wantz, THIS JOURNAL, 57, 2026 (1935).

(5) Barger and Scholz, Helv. Chim. Acta, 16, 1343 (1933).

(6) Young and Robinson, J. Chem. Soc., 275 (1933); Perkin, ibid., 815 (1916); Reichert and Hoffmann, Arch. Pharm., 274, 281 (1936).

(7) Cooke and Gulland, J. Chem. Soc., 872 (1939).

(8) Pruckner and Witkop, Ann., 554, 127 (1943).

(9) See communication following this one, THIS JOURNAL, 70, 180 (1948).

(10) Horner, Ann., 548, 119–120 (1941).