Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.26; H, 8.93.

Ethyl *trans*-β-(2-Hydroxymethylcyclohexane)propionate (VIII).—A mixture of 4.56 g. (0.02 mole) of the acid ester Vc and 4.72 g. (0.04 mole) of redistilled thionyl chloride was refluxed for 2 hr. At the end of this time, the solution was cooled and the thionyl chloride was removed overnight *in vacuo* at room temperature. The resulting crude brown oil was dissolved in 30 ml. of pure, dry dioxane and was added dropwise to a slurry of 1.13 g. of sodium borohydride in 15 ml. of pure, dry dioxane. After refluxing for 2.5 hr., the mixture was cooled in ice and 50 ml. of water was slowly added. The resulting solution was acidified to Congo Red with hydrochloric acid and extracted with three 100-ml. portions of ether. After washing the combined ether layers with water, the organic layer was dried, filtered, and evaporated to yield a residual oil which was distilled *in vacuo* to give 1.80 g. (42.1% over-all) of a colorless oil, b.p. 100–110° (0.7 mm.). Two additional distillations of this material gave pure hydroxy ester, b.p. 86° (0.07 mm.). $\tilde{\nu}_{\max}^{\mathrm{CCl_4}}$ 3525 (m, hydroxyl stretching) and 1740 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.53; H, 10.24.

***trans*-3-Oxa-4-oxobicyclo[5.4.0]undecane (III). A. From VIII.**—A mixture of 0.95 g. (4.44 mmoles) of VIII and 15 ml. of 10% sodium hydroxide solution was refluxed for 4 hr. The reaction mixture was cooled and extracted with ether; the resulting aqueous solution was acidified and re-extracted with ether. The combined ether layers from the latter extraction were washed with water to neutrality, dried, filtered, and evaporated to give an oil which upon distillation *in vacuo* gave 330 mg. (44.3%) of crude lactone as a crystalline distillate. Three recrystallizations of the white solid from benzene–petroleum ether gave pure lactone as white needles, m.p. 77.5–78.0°. $\tilde{\nu}_{\max}^{\mathrm{CCl_4}}$ 1740 cm.$^{-1}$ (lactone carbonyl); analytical bands at 1335, 1125, and 900 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.14; H, 9.58.

B. From Vb.—Into a dry 200-ml. flask was placed 4.28 g. (0.02 mole) of Vb, 10 ml. of absolute ethanol, and 100 ml. of liquid ammonia. To the rapidly stirred solution was added 4.6 g. (0.20 g.-atom) of sodium metal in small portions. Upon completion of the addition, a small amount of absolute ethanol was added to neutralize the remaining sodium. The solution was stirred until most of the ammonia had evaporated, water was added, and the solution was acidified with hydrochloric acid. The acid solution was extracted with ether, and the combined ether layers were washed with water. After the ether extract was dried, filtered, and concentrated, there remained 3.72 g. of a brownish oil which was distilled *in vacuo* to give 2.41 g. (71.7%) of a crystalline distillate, m.p. 65–72°. Recrystallization of this material from benzene–petroleum ether gave white, fluffy needles, m.p. 77–78°. A mixed melting point of this sample with a sample of the material prepared in section A gave no depression.

Dimethyl *trans*-Cyclohexane-1,2-diacetate (XI).—The diacid IX (4.00 g.) was treated with excess ethereal diazomethane as described for the preparation of Va. The residual oil was distilled *in vacuo* to yield 4.18 g. (91.8%) of a colorless liquid, b.p. 95° (0.40 mm.), $n^{26}\mathrm{D}$ 1.4600. Redistillation of a small sample of this material gave pure diester, b.p. 94° (0.40 mm.), $n^{25}\mathrm{D}$ 1.4600.[13]

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.29; H, 8.71.

Methyl Hydrogen *trans*-Cyclohexane-1,2-diacetate (XII). A mixture of 6.0 g. (0.03 mole) of IX, 9.4 ml. (10.2 g., 0.10 mole) of acetic anhydride, and 4 drops of acetyl chloride was heated on the steam bath for 3 hr. At the end of this time, the solution was cooled and 50 ml. of anhydrous methanol was added and the solution heated at reflux for 0.5 hr. After removal of the solvent mixture under reduced pressure, the residue was distilled *in vacuo* to give 4.7 g. (72.8% for the two steps) of colorless liquid, b.p. 135–139° (0.275–0.35 mm.). A small sample was redistilled to give pure acid ester, b.p. 137° (0.14 mm.), $n^{26}\mathrm{D}$ 1.4730. $\tilde{\nu}_{\max}^{\mathrm{CCl_4}}$ 1700 (s, carboxyl carbonyl) and 1740 cm.$^{-1}$ (s, ester carbonyl).

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.81; H, 8.44.

***trans*-4-Oxa-3-oxobicyclo[5.4.0]undecane (II). A. By the Sodium in Liquid Ammonia Procedure.**—A 3.50-g. (0.0163 mole) sample of XII was treated with 4.6 g. (0.20 g.-atom) of sodium, 10 ml. of absolute ethanol, and 100 ml. of liquid ammonia as described for the preparation of III. There was obtained 3.04 g. of a brownish oil which was distilled *in vacuo* to give 1.76 g. (64.2%) of colorless oil, b.p 108–113° (0.2 mm.). Redistillation of a small sample gave pure lactone, b.p. 113° (0.2 mm.), m.p. 31–32°, $n^{26}\mathrm{D}$ 1.4892 (super-cooled), $\tilde{\nu}_{\max}^{\mathrm{CCl_4}}$ 1740 cm.$^{-1}$ (s, lactone carbonyl); analytical bands at 1430, 1300, 1240, and 1015 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.65.

B. By the Bouveault-Blanc Procedure.—To a solution of 4.0 g. (0.0187 mole) of XII in 250 ml. of refluxing absolute ethanol was slowly added 9.2 g. (0.40 g.-atom) of sodium metal in small portions with rapid stirring. When all the sodium had dissolved, the alcohol was removed under reduced pressure. To the solid residue was added 250 ml. of water. With ice-cooling, the solution was acidified slowly with hydrochloric acid and extracted with three 150-ml. portions of ether. The ether extract was dried, filtered, and evaporated to give 1.5 g. of crude cyclohexane-1,2-diacetic acid, m.p. 158–162°. The remaining aqueous solution was re-extracted with two 150-ml. portions of chloroform. The combined chloroform layers were dried, filtered, and evaporated to give a yellow brown oil. Vacuum distillation of this material gave 0.63 g. (20%) of colorless oil, b.p. 108–110° (0.4 mm.), $n^{26}\mathrm{D}$ 1.4850 (super-cooled). A comparison of the infrared spectra of this material with that of the lactone prepared in section A indicated by the virtual superimposability of bands that they were identical in structure.

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[13] *After completion of this work, this diester was synthesized via an alternate route by M. E. Ali and L. N. Owen, J. Chem. Soc.,* 2111 (1958); they report for this substance b.p. 115° (0.7 mm.), $n^{19}\mathrm{D}$ 1.4625, in excellent agreement with the above work.

Synthesis of Ring C^{14}-Labeled Anthranilic and 3-Hydroxyanthranilic Acid

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The stimulus for the syntheses reported in this note arose from the desire to study the metabolism of anthranilic and 3-hydroxyanthranilic acid, the latter an important intermediate in tryptophan metabolism and a known precursor of nicotinic acid.[1]

Starting materials used in the preparation of nuclear (1,2)-C^{14}-labeled anthranilic acid (III) were butadiene and maleic anhydride (I, C^{14}-labeled at the ethylenic carbons) which, in benzene underwent Diels-Alder condensation to yield 90% of 1,2,3,6-tetrahydro-*cis*-phthalic anhydride (II).[2]

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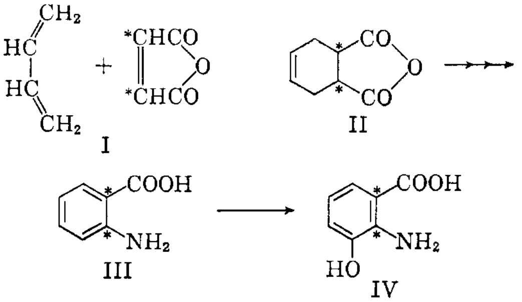
[1] H. K. Mitchell and J. F. Nyc, *Proc. Soc. Acad. Sc.*, **34**, 1 (1948).

[2] E. F. Jenkins and E. J. Costello, *J. Am. Chem. Soc.*, **68**, 2733 (1946).

Aromatization of II by the method of Newman[3] gave 70–80% yields of 1,2-C^{14}-labeled phthalic anhydride, which on reaction with concentrated ammonium hydroxide yielded 1,2-C^{14}-labeled phthalimide[4] in 95% yield. Reaction of the latter with potassium hypobromite[5] produced 1,2-C^{14}-labeled anthranilic acid (III) in 70–75% yields after a different and simpler isolation procedure than that reported.[5] Finally, persulfate oxidation of III[6] afforded 10–15% yields of the 3-hydroxy derivative (IV) which was separated by ion exchange chromatography and further purified by recrystallization as the hydrochloride. 5-Hydroxyanthranilic acid was a concomitant product of this oxidation reaction.



Experimental

Melting points, taken in a capillary, are corrected.

Ring (1,2)-C^{14}-Labeled Anthranilic Acid (III).—To 1.0 g. of maleic anhydride (cold), 8.4 mg. of maleic anhydride, C^{14}-labeled at the Π-bond carbons (I, 0.5 mc.) and 2 ml. of benzene cooled to 0° was added 2 ml. of butadiene cooled in a Dry Ice–acetone bath. The mixture was stoppered tightly and kept at room temperature for 20 hr., then excess butadiene was expelled on the steam bath. The resultant solution (benzene dilution may be necessary) was filtered and diluted with an equal volume of ligroin (b.p. 30–60°). After cooling to −15°, 1.38 g. (91%) of 1,2-C^{14}-labeled-1,2,3,6-*cis*-tetrahydrophthalic anhydride (II), m.p. 98–100° was obtained.[2]

A refluxing solution of 1.3 g. of II and 2.6 ml. of glacial acetic acid was treated during 30–40 min. (stirring), with 1.1 ml. of bromine in 2.9 ml. of acetic acid. The solution was refluxed for 18 hr., and the solvent was evaporated (bath temperature 60–70°) with a water pump aspirator. The residue was kept (stirring) at 200–210° (oil bath temperature) for 7–9 hr. The dark residue was transferred to a sublimation tube with benzene, the benzene was removed with water pump evacuation, and the residue was dried *in vacuo* over potassium hydroxide to remove hydrogen bromide. Sublimation gave 1.03 g. (79%) of 1,2-C^{14}-labeled phthalic anhydride, m.p. 129–131°.[7] Further purification is usually unnecessary. Benzene–ligroin (b.p. 30–60°) may be used for recrystallization.

To 1.0 g. of the above phthalic anhydride in a small test tube was added carefully 1.0 ml. of 12 *M* ammonium hydroxide and the mixture was dried over a free flame during 5–10 min. The residual melt was heated to 270–280° during 5–10 min. where it was kept for a few more minutes. The material was sublimed at 150°/0.5 mm. to give 0.93 g. (93%) of **1,2-C^{14}-labeled phthalimide,** m.p. 229–232°.[4]

This phthalimide (0.93 g.) was added to an ice-cold solution of 0.34 ml. of bromine in 15.4 ml. of 2 *N* potassium hydroxide. The suspension was stirred to solution (10 min.) while cooling in an ice bath. Then 0.9 g. of potassium hydroxide pellets was added and the mixture again stirred to solution while cooling. The clear solution was stirred at room temperature for 8–10 min. and warmed to 80° during 5 min. Upon cooling in an ice bath and adding 1.8 ml. of acetic acid, crude III separated and was extracted with ether. After removal of the solvent and acetic acid, *in vacuo*, the material was sublimed (105°/0.5 mm.) to give 0.65 g. (77%) of III which melted at 144–146°.[5]

1,2,C^{14}-Labeled 3-Hydroxyanthranilic Acid (IV).[8]—A stirred solution of 0.65 g. of III, 140 ml. of 2 *N* potassium hydroxide and 32 ml. of water was treated during 4 hr. with 2.6 g. of potassium persulfate in 50 ml. of water. Hydrochloric acid (40 ml. of 12 *M*) was added, the dark solution was heated on the steam bath for 30 min., and the solution was evaporated to dryness at the water pump. The residue was extracted with 30 ml. of hot absolute ethanol in five portions. The combined, filtered extracts were evaporated to dryness *in vacuo*, leaving a residue (0.5 g.) which was dissolved in 10 ml. of water and chromatographed on a column (10 × 1 cm.) of Dowex 1-acetate. The column was washed with water, then eluted with a gradient of acetic acid with 50 ml. of water in the mixing bottle into which was added 6 *N* acetic acid; 10-ml. fractions were collected. 5-Hydroxyanthranilic acid (identified by paper chromatography and fluorescence)[9] was recovered from fractions 4 and 5 and 3-hydroxyanthranilic acid (IV)[9] in fractions 8–15. These were pooled and distilled in a flash evaporator. The residue was dissolved in water and the solvent again evaporated to remove acetic acid. Recrystallization from absolute alcohol by addition of a little ether gave 50 mg. of 1,2-C^{14}-labeled-3-hydroxyanthranilic acid (V) hydrochloride, m.p. 226–227° dec., identified by comparison with authentic material, by paper chromatography and by fluorescence.[9] The filtrate was evaporated to dryness. To the residue was added 50 mg. of 3-hydroxyanthranilic acid. Recrystallization gave 60 mg. more material, m.p. 227–228° with sufficient specific activity, for metabolic studies.

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[5] M. M. S. Hoogewerf and W. A. Van Dorp, *Rec. trav. chim.*, **10**, 5 (1891).

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[8] J. F. Nyc and H. K. Mitchell, *J. Am. Chem. Soc.*, **70**, 1847 (1948).

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The Steric Course of the Acid-Promoted Addition of Acetic Acid to Norcarane

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Although the unsaturation of cyclopropane and its derivatives has long been known, investigations of the steric course of addition to cyclopropane derivatives appear to be lacking. This report describes preliminary findings of our investigation of the acid-promoted opening of the cyclopropane ring of norcarane and deals primarily with the steric course of the addition reaction.