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Syntheses of *dl*-Tetrahydroanhydrodesoxyaucubigenin and Related Compounds

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The racemic tetrahydroanhydrodesoxyaucubigenin, one of the derivatives from a glycoside, aucubin, has been synthesized using *cis-cis*-2-(2′-hydroxyethyl)-5-methoxycarbonylcyclopentanecarboxylic acid δ-lactone as an intermediate. 6, 7-Dimethoxycarbonyl-2-oxa-bicyclo[3.3.0]-octane has also been synthesized, and the mechanism of the base-catalyzed rearrangement of the naturally-derived tetrahydroanhydroaucubigenin *p*-toluenesulfonate has been elucidated.

The recent achievement of the synthesis of a number of cyclic acetals fused to a five- or six-membered ring, for example, 1-ethoxyoctahydrocyclopenta[c]pyran,[1] has prompted the present authors to attempt the synthesis of tetrahydroanhydrodesoxyaucubigenin (II),[2] one of the most important derivatives from a glycoside, aucubin (I),[2a,3] and one with a unique tricyclic acetal-ring system.

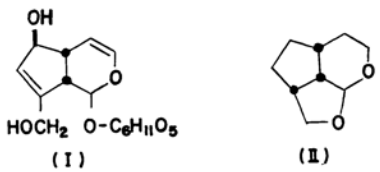

Fig. 1

In view of the previous findings,[1] an unsaturated lactone ester (X) appeared to be one of the most satisfactory intermediates for the synthesis of II, since the steric requirement (*cis-cis*) with respect to the three substituents on the cyclopentane ring in the precursor (XI) of II would be settled beyond difficulty by means of the catalytic hydrogenation of X; undoubtedly hydrogens add *cis* to the double bond from the side opposite to an allylic substituent, producing a *cis-cis* orientation. The most important and difficult problem, however, arises in the final step; that is, the lithium aluminum hydride reduction of XI must proceed selectively so as to reduce the ester group exhaustively to a primary alcohol, while reducing the lactone partially to an acetal. A controlled operation of this reduction has now been accomplished, resulting in the synthesis of racemic tetrahydroanhydrodesoxyaucubigenin (II), although in a low yield.[4] This paper will describe these results in detail, and also the syntheses of the related compounds.

The reaction of the sodio-derivative of 2-ethoxycarbonylcyclopentanone (III) with 2-iodoethyl methyl ether afforded a mixture (b. p. 130—135°C/5 mmHg) of the desired *C*-alkylated product (IV) and an undesired *O*-alkylated one (V) in a ratio of 3 : 1 (by v. p. c. analysis); the infrared spectrum showed absorption bands at 1748 and 1722 cm^{-1} due to IV and one at 1548 cm^{-1} due to V. Upon the treatment of the mixture with a boiling 0.1 molar-equivalent solution of sodium ethoxide in ethanol, the β-keto ester, a *C*-alkylated product (IV), underwent "acid-cleavage" to give diethyl 2-(2′-methoxyethyl)-adipate (VI), whereas V did not change; VI,

1) a) H. Obara, *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon Kagaku Zasshi*), **82**, 60, 62, 65 (1961); K. Kurosawa and S. Fujise, ibid., **83**, 327, (1962). b) K. Kurosawa and S. Fujise, ibid., **83**, 329 (1962).

2) a) S. Fujise, H. Obara and H. Uda, *Chem. & Ind.*, **1960**, 289; *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon Kagaku Zasshi*), **81**, 677 (1960); H. Uda, ibid., **81**, 1865 (1960). b) H. Uda, ibid., **81**, 1723 (1960).

3) a) J. Grimshaw and H. R. Juneja, *Chem. & Ind.*, **1960**, 656; A. J. Birch, J. Grimshaw and H. R. Juneja, *J. Chem. Soc.*, **1961**, 5194; M. W. Wendt, W. Haegele, E. Simonitsch and H. Schmid, *Helv. Chim. Acta*, **43**, 1440 (1960); W. Haegele, K. Kaplan and H. Schmid, *Tetrahedron Letters*, **1961**, 110. b) H. Uda, M. Maruyama, K. Kabuki and S. Fujise, *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon Kagaku Zasshi*), **85**, 279 (1964).

4) For a preliminary communication, see K. Kurosawa and S. Fujise, *Chem. & Ind.*, **1963**, 1688.

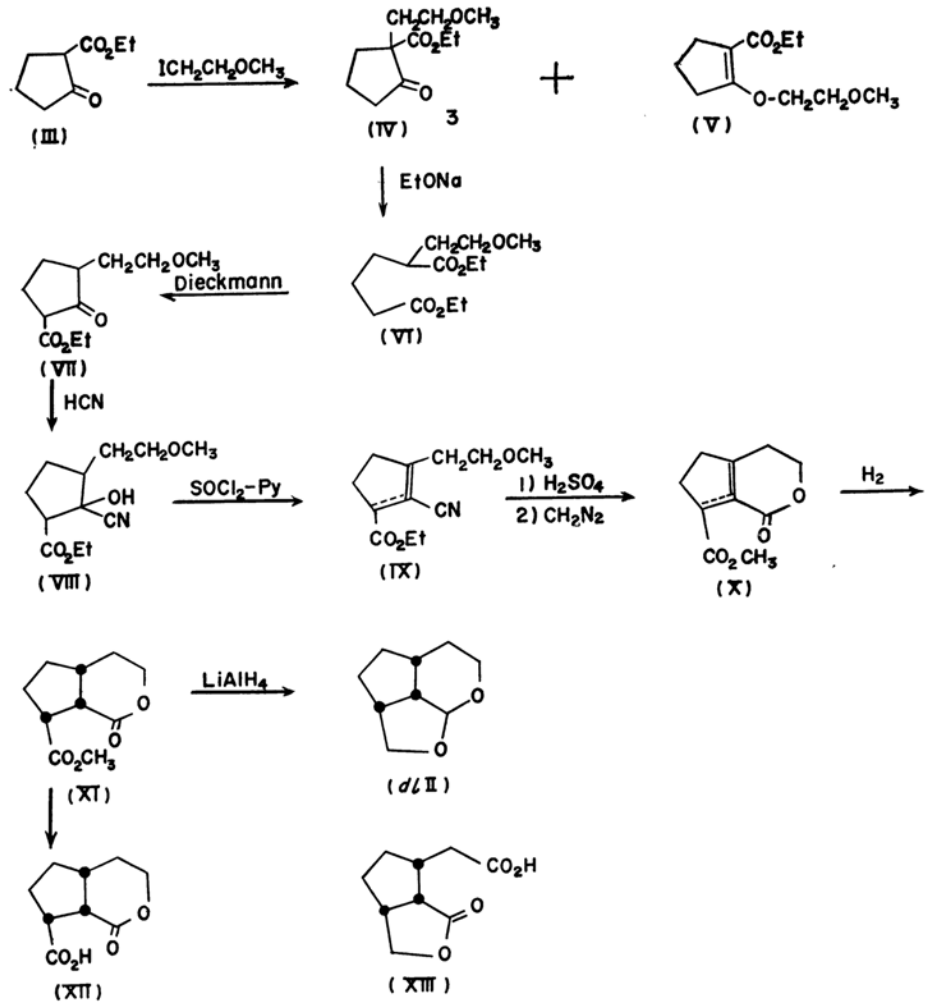

Fig. 2

b. p. 136—139°C/1 mmHg, was separated from V (distilled as a forerun) by fractional distillation through a 1 m. helix-packed column.[5] The Dieckmann cyclization of VI gave predominantly 5-ethoxycarbonyl - 2 - (2′ - methoxyethyl)cyclopen - tanone (VII), b. p. 155—162°C/3 mmHg, as expected, this was characterized by typical enol absorption bands at 1658 and 1625 cm^{-1} and a positive color test with ferric chloride. This was transformed readily into a cyanohydrin (VIII), b. p. 139—140°C/4.5 mmHg, by reaction with liquid hydrogen cyanide in the presence of a small amount of 50% potassium hydroxide; then the dehydration of VIII with thionyl chloride - pyridine gave an unsaturated nitrile ester (IX), b. p. 130—140°C/4.5 mmHg. The conversion to the desired intermediate, 2-(2′-hydroxyethyl)-5-methoxycarbonyl-Δ^1-(or Δ^5-)cyclopentenecarboxylic acid δ-lactone (X), was achieved by the hydrolysis of IX with boiling sulfuric acid - acetic acid - water, followed by the esterification of the resulting unsaturated lactone carboxylic acid with diazomethane. The pure X, obtained in a 29% yield,[6] b. p. 164—168°C/5 mmHg, ν^{neat} 1730 cm^{-1} (δ-lactone

5) 2-(2′-Acetoxyethyl) - 2 - ethoxycarbonylcyclopentanone (i)[1b] was also subjected to "acid-cleavage" reaction as one of the preliminary experiments on the introduction of the 2′-hydroxyethyl function; the product, however, was not the expected adipic acid derivative (iii), but rather an α-substituted butyrolactone derivative (ii, R = C_2H_5), b. p. 146—154°C/1.2 mmHg, ν(neat) 1768 and 1728 cm^{-1}, and the free acid (ii, R = H), m. p. 84—85°C, ν(KBr) 1760 and 1700 cm^{-1}.

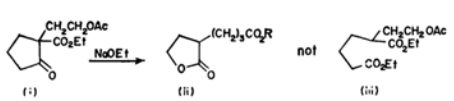

Fig. 3

6) A considerable amount of a by-product (as a low boiling fraction; b. p. 143—153°C/5 mmHg) was also isolated; it had the molecular formula of $C_{11}H_{18}O_5$ and neither a double bond nor a hydroxyl group, as was shown by infrared spectroscopy. The hydrolysis of this material gave a free carboxylic acid, $C_9H_{12}O_5$, m. p. 160—161°C. The analytical and spectral data of these compounds show the former to be the dimethyl ester of the latter, dicarboxylic acid, which possesses an oxygen-containing heterocyclic ring, but their structures have not been investigated further.

and ester) and 1648 cm^{-1} (double bond), was hydrogenated to the corresponding saturated lactone ester (XI), m. p. 72—73°C, using a platinum oxide catalyst in acetic acid, in which the stereochemistry of the three substituents on the cyclopentane ring must be *cis-cis*, as has been mentioned above.

In the final step, it is necessary to control the reduction of XI so as to discriminate each functional group to a reducing agent, lithium aluminum hydride; the ester group must be reduced exhaustively to a primary alcohol, and the lactone, partially to an acetal, in order to achieve the synthesis of II. Considering the environment of both functional groups in XI, it is obvious that the lactone would be more slowly reduced than the ester because of the steric obstruction of the ester and the hydroxyethyl moiety of the lactone ring; the ester is open to the approach of the reagent. In order to enhance this selectivity on reduction, a modified procedure was employed in which there was quite a slow reverse addition of a theoretical amount (0.75 mol.) of lithium aluminum hydride at a low temperature. Thus a mobile liquid, b. p. 112—120°C/20 mmHg, was obtained in a 10% yield; this synthetic material was identical with a sample of natural tetrahydroanhydrodesoxyaucubigenin (II) as determined by a comparison of their infrared spectra and their vapor-phase chromatographic behavior.

In addition to the above results, a few remarks regarding a comparison of synthetic lactone carboxylic acid (XII), m. p. 123—124°C, with a naturally-derived lactone carboxylic acid are appropriate. A δ-lactone structure, as XII, has been assigned on the basis of the lactone absorption band at 1755 cm^{-1} to the lactone carboxylic acid derived from the natural II by potassium permanganate oxidation in an acidic medium.[2a] The infrared spectra of the synthetic lactone carboxylic acid (XII) and its methyl ester (XI) are, however, completely different from those of the naturally-derived compounds, including the lactone carbonyl absorption which is at 1715 in XII and at 1725 cm^{-1} in XI, whereas it is at 1755 and 1766 cm^{-1} in the natural lactone carboxylic acid and methyl ester respectively. Consequently, the structure of the natural lactone carboxylic acid should be revised to the formula XIII with γ-lactone.[7]

7) The nuclear magnetic resonance spectrum of the natural lactone carboxylic acid also supports the structure XIII. Private communication of Dr. W. H. Tallent, G. D. Searle and Co. Two protons, H_A and H_B, attached to the carbon atom bearing lactone hydroxyl show a AB-type quartet at ca. δ=4.2 p.p.m., each peak of which is further split into a doublet by coupling with an adjacent proton, H_C (J_{AB}=10, J_{AC}=9—10, and J_{BC}=3—4 c.p.s.).

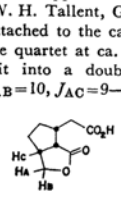

Fig. 4

Finally, as a part of the synthetic work on the aucubin derivative, the synthesis of 6, 7-dimethoxycarbonyl-2-oxa-bicyclo[3.3.0]octane (XXIII) should be mentioned.

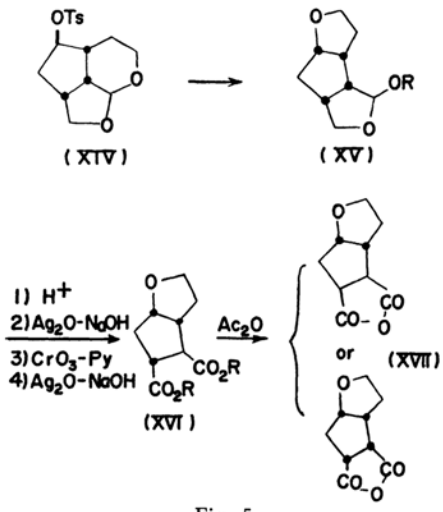

Fig. 5

It has been also reported that tetrahydroanhydroaucubigenin *p*-toluenesulfonate (XIV), when treated with alcoholic potassium hydroxide or sodium ethoxide, underwent acetal ring opening and a new oxygen-containing ring formation to give a compound XV, the structure of which was assumed to be that of a 2-oxa-bicyclo[3.3.0]octane derivative according to the successive transformation of XV into a succinic-type anhydride[8] (XVII), as is shown in Fig. 5; this unusual rearrangement has been explained in terms of the back-side attack of the ring-oxygen atom in the six-membered ring of XIV on the *p*-toluenesulfonyloxy group, facilitated by the attack of the hydroxy or ethoxy anion on the acetal carbon atom.[3b,9] It appeared, however, that the previous results were not sufficient to lead to a definite conclusion concerning the mechanism of rearrangement and the structure of product; hence, the final confirmation should be made by the synthesis of either compound from XV to XVII.

8) For the same type of epimerization involving one carboxyl group in the *trans*-cyclopentane-1, 2-dicarboxylic acid derivative during anhydride formation, see R. B. Bates, E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **80**, 3413 (1958), and Refs. 2a and 10.

9) The alternative mechanism, in which another oxygen atom (in the five-membered ring) participates in this reaction, giving a bridged compound (iv), has been excluded because a dicarboxylic acid corresponding to XVI (R=H) would have to form a glutaric-type anhydride (v).

Fig. 6

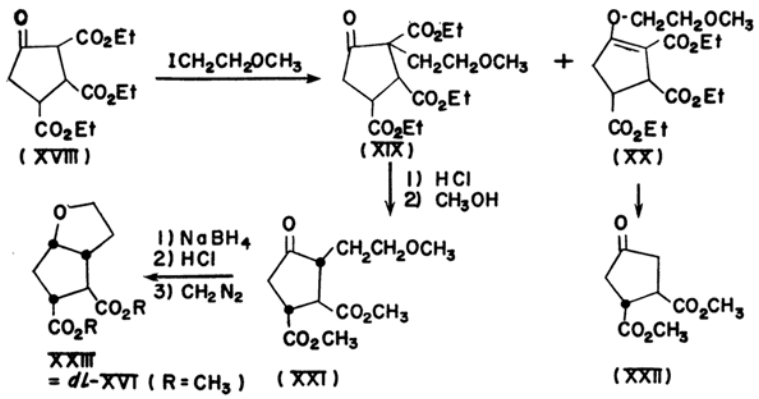

Fig. 7

The condensation of the sodio-derivative of 2, 3, 4-triethoxycarbonylcyclopentanone (XVIII)[10] with 2-iodoethyl methyl ether afforded a mixture of a *C*-alkylated (XIX) and an *O*-alkylated product (XX), in roughly equal amounts (as determined by v. p. c. analysis). The hydrolysis of them with boiling 6 N hydrochloric acid, followed by the esterification of the resulting carboxylic acid using methanol, gave a mixture of the desired compound (XXI) and a keto diester (XXII); these were readily separated by fractional distillation. XXI, b. p. 145—155°C/1.5 mmHg, was characterized by the formation of 2, 4-dinitrophenylhydrazone, $C_{18}H_{22}O_9N_4$, m. p. 123—124°C, and the relative configuration of three substituents must be a thermodynamically more stable or sterically more favorable *trans-trans* arrangement.

The reduction of XXI with sodium borohydride proceeded stereospecifically to produce a single hydroxy diester with *cis* hydroxyl to the adjacent methoxyethyl side chain, which was then transformed into a dicarboxylic acid (XXIII, R=H), accompanied by a simultaneous ring closure, by being refluxed in concentrated hydrochloric acid; subsequent esterification with diazomethane furnished 6, 7-dimethoxycarbonyl-2-oxa-bicyclo[3.3.0]-octane (XXIII, $R=CH_3$). The synthetic material (XXIII, $R=CH_3$) was identical with a sample of natural diester (XVI, $R=CH_3$) as was shown by vapor-phase chromatography and infrared spectroscopy. These results provide convincing evidence of the correctness of the proposed mechanism of transformation from XIV to XV, and also of the assigned structure for XVI; XVI must have a *trans-anti-cis*[11] configuration, and the epimerization of the acetal substituent in XV must take place during the oxidation sequence to XVI.

10) K. Kurosawa and H. Obara, This Bulletin, **39**, 525 (1966).
11) In this designation the relationship of the two carboxyl groups attached to the cyclopentane ring is given first.

Experimental

2-Chloroethyl Methyl Ether.—To a mixture of 500 g. (6.6 mol.) of ethylene glycol monomethyl ether and 500 ml. of pyridine, there was added 1 kg. (8.4 mol.) of thionyl chloride dropwise with stirring and ice cooling; after the mixture had been allowed to stand at room temperature for 48 hr., 500 ml. of water was added. The resulting mixture was extracted with ether three times, and the combined extracts were washed with 10% aqueous sodium hydroxide, dried over calcium chloride, and freed from ether. The residual liquid was distilled through a short fractional column to give 498 g. (80%) of 2-chloroethyl methyl ether, b. p. 89—90°C.

2-Iodoethyl Methyl Ether.—A solution of 438 g. of 2-chloroethyl methyl ether and 1 kg. of sodium iodide in 1 l. of dry acetone was refluxed for 50 hr.; the reaction mixture was then poured into ice water and extracted with ether. The extract was successively washed with aqueous sodium thiosulfate, water, and saturated sodium chloride solution, dried over calcium chloride, and freed from ether. Distillation of the residual liquid gave 782 g. (90%) of 2-iodoethyl methyl ether, b. p. 103—105°C.

Condensation of 2-Ethoxycarbonylcyclopentanone (III) with 2-Iodoethyl Methyl Ether.—To a suspension of 29 g. of finely-granulated sodium metal in 1 l. of anhydrous toluene was added 190 g. of 2-ethoxycarbonylcyclopentanone (III) dropwise with vigorous stirring; the mixture was then heated on an oil bath, while being continuously stirred, until all of the sodium was consumed, after about 5 hr. Then 323 g. of 2-iodoethyl methyl ether was added to the above jelly-like solution of the sodio-derivative of III, and the reaction mixture was refluxed for 10 hr. After cooling, the mixture was worked up by dilution with water, acidification with hydrochloric acid, and extraction in the usual manner to give a crude condensation product. Distillation in vacuo gave 218 g. (84%) of a mixture of two products, b. p. 130—135°C/5 mmHg. The mixture consisted of a *C*-alkylated (IV) and an *O*-alkylated product (V) in the ratio of about 3 : 1, as was determined by v. p. c. on a 3 m. silicone DC 550 column, there were two peaks at retention times of 25 min. (major) and 46 min. (minor) (200°C;

hydrogen flow 80 ml./min.). The major product (IV) gave 2, 4-dinitrophenylhydroazone, m. p. 69.5—70.5°C (from dilute ethanol), according to the usual procedure.

Found: C, 51.54; H, 5.62; N, 13.69. Calcd. for $C_{17}H_{22}O_7N_4$: C, 51.77; H, 5.62; N, 14.21%.

Diethyl 2-(2'-Methoxyethyl)adipate (VI).—The mixture of IV and V from the preceding experiment (624 g.) was treated with a sodium ethoxide solution prepared from 6.7 g. of metallic sodium and 1 l. of anhydrous ethanol; the resulting mixture was refluxed for 6 hr. The mixture was then neutralized with ethanolic hydrogen chloride and heated again for an additional 2 hr. The ethanol was removed by distillation, and the residual oil was poured into ice water and extracted with ether three times. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and freed from ether to give 467 g. of the crude material. Fractional distillation in vacuo through a 1 m. helix-packed column gave, after a forerun of ca. 40 g., 425 g. (57%) of pure diethyl 2-(2'-methoxyethyl)-adipate (VI), b. p. 136—139°C/1 mmHg, n_D^{20} 1.4471, d_4^{20} 1.024, M. R. Obs.: 67.95; Calcd.: 67.19.

Found: C, 60.15; H, 9.55. Calcd. for $C_{13}H_{24}O_5$: C, 59.95; H, 9.29%.

5-Ethoxycarbonyl-2-(2'-methoxyethyl)cyclopentanone (VII).—To a suspension of 39 g. of finely-granulated sodium metal in 1 l. of dry benzene was added 425 g. of VI dropwise with efficient stirring; the reaction mixture was then warmed at 80°C for 2 hr., poured into cold 10% aqueous acetic acid, and extracted with benzene. The organic layer was thoroughly washed with saturated brine, dried over anhydrous sodium sulfate, and freed from benzene. The residual liquid was distilled in vacuo to give 227 g. (62%) of β-keto ester (VII), b. p. 155—162°C/3 mmHg, n_D^{18} 1.4600, d_4^{18} 1.073, M. R. Obs.: 54.58; Calcd.: 54.11, which gave a purple color with ferric chloride.

Found: C, 61.11; H, 8.55. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%.

VII (5 g.) was hydrolyzed and decarboxylated by refluxing with 10% sulfuric acid; it thus gave 2.2 g. (67%) of 2-(2'-methoxyethyl)cyclopentanone, b. p. 104—108°C/24 mmHg, ν^{neat} 1755 cm^{-1}, n_D^{31} 1.4964, d_4^{31} 0.9799, M. R. Obs.: 38.37; Calcd.: 38.59, which in turn gave 2, 4-dinitrophenylhydrazone, m. p. 123—124°C.

Found: C, 52.31; H, 5.82; N, 17.37. Calcd. for $C_{14}H_{18}O_5N_4$: C, 52.17; H, 5.63; N, 17.38%.

This 2-(2'-methoxyethyl)cyclopentanone was also obtained from IV by hydrolysis and decarboxylation.

2-(2'-Methoxyethyl)-5-ethoxycarbonylcyclopentenylnitrile (IX).—Freshly-prepared liquid hydrogen cyanide (25 ml.) and a few drops of a 50% potassium hydroxide solution were added to 20 g. of the β-keto ester (VII) with ice cooling and vigorous stirring, and the reaction mixture was stored at 0°C for 20 hr. and carefully acidified with 80% phosphoric acid. The excess hydrogen cyanide was expelled under reduced pressure. Distillation of the residual liquid gave 18 g. of 5-ethoxycarbonyl-2-(2'-methoxyethyl)cyclopentanone cyanohydrin (VIII), b. p. 139—140°C/4.5 mmHg.

The above cyanohydrin (VIII) (18 g.) was dissolved in 20 ml. portions of anhydrous pyridine and benzene and treated with 18.5 g. (11 ml.) of thionyl chloride at 0°C. The reaction mixture was then allowed to stand at the same temperature for 20 hr., poured into ice water, and extracted with benzene. The benzene extracts were washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and water, dried over anhydrous sodium sulfate, and freed from benzene to give a crude product. Distillation in vacuo gave 13.2 g. (79%) of an unsaturated nitrile ester (IX), b. p. 130—140°C/4.5 mmHg, n_D^{18} 1.4799, d_4^{18} 1.075, M. R. Obs.: 58.32. Calcd.: 58.06.

Found: C, 63.71 (low); H, 7.51; N, 6.47. Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27%.

2-(2'-Hydroxyethyl)-5-methoxycarbonylcyclopentenylcarboxylic Acid Lactone (X).—The unsaturated nitrile ester (IX) (13.2 g.) was dissolved in a solution of 23 ml. of concentrated sulfuric acid, 70 ml. of acetic acid, and 35 ml. of water, and the reaction mixture was refluxed for 15 hr. After cooling, the reaction mixture was diluted with ca. 130 ml. of water and extracted with ether. The ether extract was evaporated to dryness under reduced pressure; then the residual oil was dissolved in a dilute sodium hydroxide solution prepared from 20 g. of sodium hydroxide and 160 ml. of water. This solution was refluxed for 3 hr., acidified with concentrated hydrochloric acid, evaporated to dryness, and finally extracted with ethyl acetate. The ethyl acetate extract was treated with excess diazomethane in ether. The solvent was removed by distillation, and the residual liquid was fractionally distilled in vacuo through a short fractional column. After a forerun of 7 g. (b. p. 143—153°C/5 mmHg), the fraction (5.5 g.) was collected at b. p. 164—168°C/5 mmHg. This fraction consisted mainly of the desired unsaturated lactone ester (X). n_D^9 1.5042.

Found: C, 60.30 (low); H, 6.22. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17%.

The forerun showed the following physical properties: n_D^{13} 1.4775, d_4^{13} 1.290, M. R. Obs.: 54.29; Calcd.: 53.55.

Found: C, 57.51; H, 7.29. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.01%.

The hydrolysis of this material with boiling dilute hydrochloric acid gave a crystalline substance, which was then recrystallized from chloroform. M. p. 160—161°C. There was neither hydroxy nor double bond absorption in the infrared spectrum.

Found: C, 53.61; H, 6.07. Calcd. for $C_9H_{12}O_5$: C, 53.99; H, 6.04%.

2-(2'-Hydroxyethyl)-5-methoxycarbonylcyclopentylcarboxylic Acid Lactone (XI).—The unsaturated lactone ester (X) (3.8 g.) in 25 ml. of acetic acid was hydrogenated using a platinum oxide catalyst at atomospheric pressure. A total of 375 ml. (70% of the theoretical amount) of hydrogen was absorbed. Filtration of the catalyst, followed by evaporation of the acetic acid to dryness, afforded a viscous liquid which was then distilled in vacuo to give 2.5 g. (65%) of a saturated lactone ester (XI), b. p. 163—167°C/3.5 mmHg, n_D^{13} 1.4886, d_4^{13} 1.220, M. R. Obs.: 46.87. Calcd.: 47.29. This distilled material gradually crystallized upon standing; it was recrystallized from ethyl acetate-petroleum ether to give pure XI, m. p. 72—73°C.

Found: C, 60.49; H, 7.48. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.

***dl*-Tetrahydroanhydrodesoxyaucubigenin (II).**—A solution of 0.303 g. (7.95 mmol.) of lithium aluminum hydride in 20 ml. of anhydrous ether was added dropwise at −15 to −18°C to a stirred solution of 2.1 g. (10.6 mmol.) of the crystalline saturated lactone ester (XI) in 20 ml. of anhydrous ether; the reaction mixture was

then stored at 0°C overnight. Dilute sulfuric acid (10%) was slowly added to the reaction mixture with cooling and stirring until the solution became slightly acidic (Congo red); the organic layer was separated, and the water layer was extracted with ether three times. The combined ether extracts were then washed with water, dried over anhydrous sodium sulfate, and freed from ether. Distillation of the residual liquid in vacuo gave 0.15 g. (10%) of colorless *dl*-tetrahydroanhydrodesoxyaucubigenin (II), b. p. 112—120°C/15 mmHg, n_D^{19} 1.4987, d_4^{19} 1.124 (the reported values for the natural II: n_D^{20} 1.4961, d_4^{20} 1.1249),[2b] M. R. Obs.: 40.30. Calcd.: 40.43. Analysis by v. p. c. using a silicone DC 550 column indicated that this product was essentially pure; its behavior on this column (at 150°C) exactly matched that of pure natural tetrahydroanhydrodesoxyaucubigenin. The infrared spectrum of a sample of the synthetic product was completely indistinguishable from that of the authentic natural product II.

Found: C, 70.66; H, 9.59. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15%.

2-(2′-Hydroxyethyl)-5-carboxycyclopentylcarboxylic Acid (XII).—The saturated lactone ester (XI) (4 g.) was hydrolyzed by refluxing with 30 ml. of 1.2 N hydrochloric acid for 3 hr.; the solution was then evaporated. The separated crystalline solid was collected and recrystallized from ethyl acetate-petroleum ether to give 1.5 g. (40%) of a lactone carboxylic acid (XII), m. p. 123—124°C.

Found: C, 59.03; H, 6.64. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.54%.

The infrared spectrum of this material was completely different from that of the lactone carboxylic acid derived from the natural II.

2-(3′-Ethoxycarbonylpropyl)butyrolactone (ii, R=C_2H_5) and the Free Acid (ii, R=H).—A solution of 24 g. of 2-(2′-acetoxyethyl)-2-ethoxycarbonylcyclopentanone (i)[1b] in 30 ml. of anhydrous ethanol containing 1.5 g. of sodium ethoxide was refluxed for 2 hr. The ethanol was then removed by distillation, and the residue was poured into ice water and extracted with ether. The ether extract was then washed with water, dried over anhydrous sodium sulfate, and freed from ether. Distillation of the residual liquid in vacuo gave 16 g. of a butyrolactone derivative (ii, R=C_2H_5), b. p. 146—154°C/1.2 mmHg, n_D^{12} 1.4574, d_4^{12} 1.087, M. R. Obs.: 49.25. Calcd.: 49.49.

Found: C, 59.88; H, 8.04. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.04%.

Hydrolysis of 2 g. of this material by refluxing with 30 ml. of 4 N hydrochloric acid, followed by recrystallization of the resulting semi-solid product from benzene, afforded 1.1 g. (64%) of 2-(2′-hydroxyethyl)adipic acid γ-lactone (ii, R=H), m. p. 84—85°C.

Found: C, 55.24; H, 6.92. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03%.

Condensation of 2, 3, 4-Triethoxycarbonylcyclopentanone (XVIII) with 2-Iodoethyl Methyl Ether.—The sodio-derivative of XVIII was prepared from 21.5 g. of keto triester (XVIII)[10] and 3.5 g. of finely-granulated sodium metal in 150 ml. of dry xylene according to the usual procedure. To this solution there was added dropwise 30 g. of 2-iodoethyl methyl ether with stirring; the reaction mixture was then refluxed for 10 hr., and worked up in the usual manner, using benzene for extraction of the product to give 20 g. of a mixture of a *C*-alkylated and an *O*-alkylated product (XIX and XX) in roughly equal amount (as determined by v. p. c. analysis on a silicone DC 550 column), b. p. 160—195°C/2.0 mmHg.

3,4-Dimethoxycarbonyl-2-(2′-methoxyethyl)cyclopentanone (XXI).—The mixture of XIX and XX obtained from the preceding experiment (20 g.) was hydrolyzed by boiling it in 150 ml. of 6 N hydrochloric acid for 4 hr. After removal of the hydrochloric acid and almost all of the water under reduced pressure, the oily residue was dissolved in anhydrous methanol containing a small amount of hydrogen chloride; the resulting solution was then refluxed for 36 hr. The methanol was removed by distillation, and the residual liquid was distilled in vacuo. After a forerun of 6 g. (major fraction, b. p. 122—129°C/1.5 mmHg), which consisted mainly of 3, 4-dimethoxycarbonylcyclopentanone (XXII), the minor fraction (2.5 g.) was collected at a boiling point of 145—155°C/1.5 mmHg. This fraction was the essentially-pure desired compound, 3, 4-dimethoxycarbonyl-2-(2′-methoxyethyl)cyclopentanone (XXI), as was shown by v. p. c. on a silicone DC 550 column. The 2, 4-dinitrophenylhydrazone of this material was prepared in the usual manner in a good yield. It had a melting point of 123—124°C.

Found: C, 49.83; H, 5.04; N, 12.59. Calcd. for $C_{18}H_{22}O_9N_4$: C, 49.31; H, 5.06; N, 12.78%.

***trans-anti-cis*[11]-6, 7-Dimethoxycarbonyl-2-oxabicyclo[3. 3. 0]octane (XXIII, R=CH_3) (*dl*-XVI, R=CH_3).**—A solution of 1.0 g. of XXI in a small amount of methanol was added to a solution of 0.55 g. of sodium borohydride in 4 ml. of methanol containing a trace of sodium hydroxide; the mixture was then refluxed for 4 hr. After the methanol had been removed, the residual solid was warmed with 5 ml. of concentrated hydrochloric acid on a steam bath for 2 hr., and then dried up to give a paste-like dicarboxylic acid (XXIII, R=H). This material, without further purification, was dissolved in a small amount of ethyl acetate and treated with excess ethereal diazomethane. The solvents were removed by distillation, and the residual liquid was distilled in vacuo to give 0.25 g. (30%) of the diester (XIII, R=CH_3), b. p. 123—125°C/1.0 mmHg. The infrared spectrum of a sample of the product collected by v. p. c. using a silicone DC 550 column was completely identical with that of a specimen of the naturally-derived diester (XVI, R=CH_3), and the v. p. c. behaviors of the two samples were also identical. An analytical sample was prepared by v. p. c.

Found: C, 57.56; H, 7.21. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07%.

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