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Synthesis of (±)-Tetrahydroanhydroaucubigenone and (±)-Tetrahydroanhydroaucubigenin[1]

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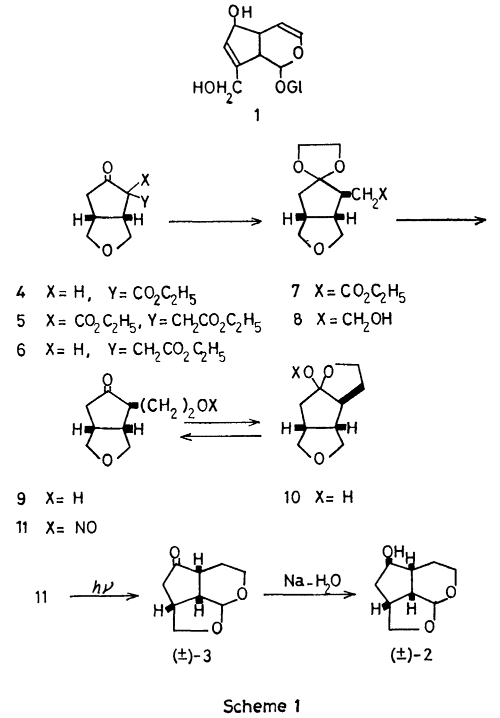
The racemate of tetrahydroanhydroaucubigenone (**3**), one of the related compounds of aucubin, was synthesized by the photoirradiation of 6-[2-(nitrosooxy)ethyl]-3-oxabicyclo[3.3.0]octan-7-one. (±)-Tetrahydroanhydroaucubigenin was also obtained by reduction of (±)-**3** with sodium in moist ether.

Tetrahydroanhydroaucubigenin (**2**), mp 85 °C, $[\alpha]_D^{19.6}$ +51.5° (ethanol), and its oxidation product, tetrahydroanhydroaucubigenone (**3**), mp 77—78 °C, $[\alpha]_D^{17}$ −41.3° (ethanol), have been known to be the key compounds for the determination of aucubin (**1**).[2] These compounds have been already obtained by Karrer[3] and Fujise[4] in 1946 and 1953, independently, and the correct structures were established by Fujise *et al.*[5] in 1960. However, the synthesis of **2** and **3** have not been accomplished yet. In this paper, we wish to report the synthesis of the racemates of **2** and **3** by the following scheme.



Scheme 1

6-Ethoxycarbonyl-6-ethoxycarbonylmethyl-3-oxabicyclo[3.3.0]octan-7-one (**5**) was obtained with a small amount of *O*-alkylated compound by alkylation of the sodio derivative of *cis*-6-ethoxycarbonyl-3-oxabicyclo[3.3.0]octan-7-one (**4**) with ethyl bromoacetate in toluene. Hydrolysis and decarboxylation of **5** with 6 M hydrochloric acid, followed by esterification, afforded 6-ethoxycarbonylmethyl-3-oxabicyclo[3.3.0]octan-7-one (**6**) in a 50% yield. This compound does not change by treatment with sodium ethoxide, so it is assumed that it has a more stereochemically favorable *cis-trans* (1,5- and 5,6-position) configuration. After acetalization of **6** with ethylene glycol, the acetal (**7**) was reduced into the alcohol (**8**) with lithium aluminium hydride in tetrahydrofuran in a 89% yield. Deacetalization of **8** by treatment with dilute hydrochloric acid or *p*-toluenesulfonic acid in acetone afforded a mixture of 6-(2-hydroxyethyl)-3-oxabicyclo[3.3.0]octan-7-one (**9**) and its intramolecular hemiacetal (**10**) in a 76% yield. The hemiacetal (**10**) is easily oonverted into the keto alcohol (**9**) by treatment with dilute hydrochloric acid. 6-[2-(Nitrosooxy)ethyl]-3-oxabicyclo[3.3.0]octan-7-one (**11**), a pale green unstable viscous oil, was obtained by the nitrosation of **9** with a mixture of sodium nitrite and dilute sulfuric acid in a 30% yield.

The irradiation of **11** was carried out in a benzene solution under a nitrogen atmosphere at 0 °C using a high-pressure 500 W mercury arc. After irradiation, the benzene was removed *in vacuo* and the residue was chromatographed on silica gel to give (±)-tetrahydroanhydroaucubigenone ((±)-**3**), colorless prisms, mp 57—57.5 °C. The IR spectrum of this compound in carbon tetrachloride was identical with that of the natural sample. Since the *cis-cis* configuration of the ring junction of **3** is already confirmed,[6] it can be assumed that the photoisomerization at 6-position occurred simultaneously with the photochemical ring closure of **11**. The reduction of (±)-**3** was carried out by considering the configuration of the hydroxyl group of **2**. Fujise *et al.*[7] previously reported that the epimer of **2** was obtained as an oil by reduction of **3** with lithium aluminium hydride in ether, and they have referred to the mechanism of its stereospecific reduction. We achieved the synthesis of ((±)-**2**), mp 74.5—75 °C, in a 46% yield by reduction of (±)-**3** with sodium in moist ether instead of lithium aluminium hydride. The IR spectrum was identical with that of the natural sample.

Experimental

All the boiling and melting points are uncorrected.

6-Ethoxycarbonyl-6-ethoxycarbonylmethyl-3-oxabicyclo[3.3.0]octan-7-one (5). To a suspension of 11.5 g of sodium metal in 240 ml of dry toluene was added 92.5 g of *cis*-6-ethoxycarbonyl-3-oxabicyclo[3.3.0]octan-7-one (**4**)[8] dropwise with efficient stirring. The stirred mixture was heated on an oil bath until all the sodium was consumed. Then 83.5 g of ethyl bromoacetate was added to the solution at room temperature, and the mixture was refluxed for 4 h. Upon cooling, the mixture was poured into 150 ml of aqueous 10% acetic acid and the toluene layer was washed with aqueous NaHCO$_3$ and water, dried over Na$_2$SO$_4$, and freed from toluene to give a viscous liquid. Distillation of the residue under reduced pressure afforded 113.8 g (85%) of **5** containing a small amount of

O-alkylated by-product, bp 163—169 °C/6 mmHg, MS *m/e* 284 (M^+); IR (neat) 1755 and 1730 cm^{-1} (C=O). The additional absorption bands at 1635 and 1685 cm^{-1} can be attributed to an *O*-alkylated by-product. Found: C, 58.72; H, 7.08%. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09%.

6-Ethoxycarbonylmethyl-3-oxabicyclo[3.3.0]octan-7-one (6). The keto ester (**5**) (50 g), containing a small amount of the *O*-alkylated product, was hydrolyzed in 150 ml of aqueous 6 M HCl under boiling for 5 h. After removal of most of the HCl and water under reduced pressure, a mixture of 100 ml of ethanol, 50 ml of toluene, and 0.1 ml of concd H_2SO_4 was added to the oily residue, and the mixture was distilled slowly at atmosphere pressure. The esterification was completed by the redistillation with 100 ml of ethanol and 50 ml of toluene. After the solvent was removed *in vacuo*, the oily residue was extracted with ether, and the ether layer was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and freed from ether to give a viscous oil. Distillation of the residue in reduced pressure afforded **6**, bp 140—144 °C/4 mmHg, in a 75% yield. MS *m/e* 212 (M^+); IR (neat) 1730 cm^{-1} (C=O). Found: C, 61.89; H, 7.44%. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%. 3-Oxabicyclo[3.3.0]octan-7-one (0.5 g), bp 107—109 °C/14 mmHg (lit,[8]) bp 118—119 °C/17 mmHg), 2,4-dinitrophenylhydrazone, mp 144—145 °C (lit,[8]) mp 144—145 °C), was obtained as a minor fraction, which was derived from the *O*-alkylated product.

6-(2-Hydroxyethyl)-3-oxabicyclo[3.3.0]octan-7-one (9). A mixture of 30 g of 6-ethoxycarbonylmethyl-3-oxabicyclo[3.3.0]-octan-7-one (**6**), 9.7 g of ethylene glycol, 160 ml of dry benzene, and 60 mg of *p*-toluenesulfonic acid was refluxed on an oil bath for 3 h. Then, most of the water was removed azeotropically at atmospheric pressure. After removal of the solvent, the residue was taken up in ether and worked up in the usual manner to afford 28.1 g (78%) of ethylene acetal (**7**), bp 150—153 °C/3 mmHg, MS *m/e* 256 (M^+). To a mixture of 80 ml of dry THF and 2.5 g of $LiAlH_4$ was added 28.1 g of the ethylene acetal (**7**) over a period of 1 h with stirring on an ice bath and warmed at 40—50 °C for 2 h. Then, 20 ml of water was added cautiously to decompose the unreacted $LiAlH_4$. The THF layer was separated by decantation and freed from THF to give an oily residue. Distillation of the residue in diminished pressure afforded 6-(2-hydroxyethyl)-3-oxabicyclo[3.3.0]octan-7-one ethylene acetal (**8**) (18.9 g, 80%), bp 146—151 °C/2 mmHg, MS *m/e* 214 (M^+). A mixture of 18.2 g of **8** and 60 ml of aqueous 0.2 M HCl was warmed at 50—60 °C for 2 h. After neutralization with solid $NaHCO_3$, it was concentrated to about one-fifth of its original volume and extracted with ether. The ether layer was worked up by the usual manner and distilled to give 10.8 g (75%) of 6-(2-hydroxyethyl)-3-oxabicyclo[3.3.0]octan-7-one (**9**), bp 145—146 °C/3 mmHg, MS *m/e* 170 (M^+), IR (neat) 3450 cm^{-1} (OH) and 1736 cm^{-1} (C=O). Found: C, 62.72; H, 8.40%. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%. 2,4-Dinitrophenylhydrazone, mp 151—152 °C. Found: C, 51.26; H, 5.21; N, 15.72%. Calcd for $C_{15}H_{17}O_6N_4$: C, 51.57; H, 4.91; N, 16.04%.

6-[2-(Nitrosooxy)ethyl]-3-oxabicyclo[3.3.0]octan-7-one (11). To a mixture of 2.0 g of **9**, 7.5 g of $NaNO_2$, and 10 ml of water, was added a mixed solution of 2.5 ml of concd H_2SO_4 and 1 ml of water dropwise with efficient stirring in an ice–salt bath over a period of 1 h. The reaction mixture was then extracted with ether and the ether layer was worked up in the usual manner. Distillation of the residue in reduced pressure afforded 0.7 g (30%) of **11**, bp 100—102 °C/2 mmHg, IR (neat) 1735 cm^{-1} (C=O), 1640, 1600, and 790 cm^{-1} (N=O and N–O). This green unstable oil was used immediately in the subsequent photoirradiation.

(±)-Tetrahydroanhydroaucubigenone ((±)-3). A solution of 0.4 g of **11** in 110 ml of dry benzene was irradiated with stirring for 15 h under a nitrogen atmosphere at 0 °C by a high-pressure 500 W mercury arc using a CS-054 filter (corning glass works). After irradiation, the solvent was removed *in vacuo*, and the residue was chromatographed on a column of silica gel. Elution with CCl_4–ethyl acetate gave crude (±)-**3** (36 mg) as an oil. Recrystallization from benzene–petroleum ether afforded (±)-**3** (21 mg, 5.7%), mp 57.5 °C. MS, *m/e* 168 (M^+), 139, 110, 83, 69 (base), 55, and 41; IR (CCl_4), ν_{max} 2970, 2900, 1748 (strong), 1175, 1148, 1100, 1065, 1040, 980, and 945 cm^{-1}. The IR spectrum of this compound in CCl_4 was identical with that of the natural sample.

(±)-Tetrahydroanhydroaucubigenin ((±)-2). To a mixture of 12.2 mg of (±)-**3**, 0.02 ml of water, and 3 ml of ether, was added slowly 20 mg of sodium metal in limited amounts over a period of 15 min at 0 °C. The subsequent alternate addition of 0.02 ml of water and 20 mg of sodium metal was continued until the disappearance of the spot of (±)-**3** has been confirmed by TLC. Then water was cautiously added to the reaction mixture and the ether layer was thoroughly washed with saturated brine, dried, and evaporated to leave a crystalline residue, which on recrystallization from petroleum ether–benzene yielded (±)-**2** (5.6 mg, 46%) as colorless prisms, mp 74.5—75 °C. IR (CCl_4), ν_{max} 3600, 3450, 1403, 1153, 1138, 1077, 1060, 1040, 1004, and 972 cm^{-1}. The IR spectrum of this compound in CCl_4 was identical with that of the natural sample.

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