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The preparation of some derivatives of glycyrrhetic acid and oleanolic acid

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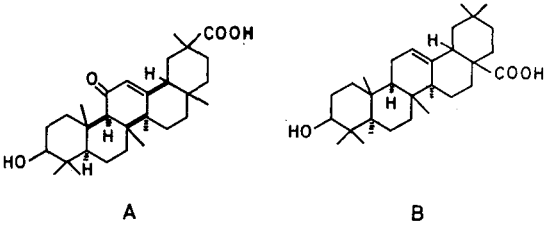
Some new derivatives of glycyrrhetic acid and oleanolic acid were prepared and characterized. Various combinations of the modified and normal functional groups were synthesized as required for a separate study of the uncoupling activities of glycyrrhetic acid and oleanolic acid. The hydroxyl functions of these two acids were modified to β-carboxypropionyl, acetyl and β-methoxycarbonylpropionyl esters. The carboxyl function of glycyrrhetic acid was converted to amide, *p*-amidobenzoic acid, *o*-amidobenzoic acid and the glycine conjugate of the acid. 11-Deoxy (glycyrrhetic acid) and 9,11-dehydro-11-deoxo (from both acids) analogues were prepared. 11-Oxo analogues of oleanolic acid were synthesized as well as the methyl esters.

THE acid, 18β-glycyrrhetic acid (glycyrrhetinic acid, 3β-hydroxy-11-oxo-5α,18β-olean-12-en-30-oic acid; I) is the aglycone of glycyrrhizin (glycyrrhizic acid), a diglucuronide present in liquorice. This pentacyclic triterpenoid acid possesses some striking pharmacological properties, inhibiting diuresis (so-called "mineralcorticoid" activity) and when administered as the 3-*O*-hemisuccinate ester to man, promoting the healing of stomach ulcers (Parke & Williams, 1962; Doll, Hill & others, 1962).



A B

FIG. 1. Structure of: A. Glycyrrhetic acid. B. Oleanolic acid.

It also exhibits anti-inflammatory activity in laboratory animals (Finney & Somers, 1958; Kraus, 1960; Aleshinskaya, Aleshkina & others, 1964; Tangri, Seth & others, 1965) and, in common with many other anti-inflammatory drugs, uncouples oxidative phosphorylation in liver mitochondria and in extrahepatic tissues such as cartilage (Whitehouse & Haslam, 1962).

The relation between the chemical structure and uncoupling activity of glycyrrhetic acid has been analysed by Whitehouse, Dean & Halsall (1967). For this purpose, some novel derivatives of glycyrrhetic acid and oleanolic acid (3β-hydroxyolean-12-en-28-oic acid; II) were required and their preparation and characterization are now described.

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Experimental

MATERIALS

Oleanolic acid, and purified 18α- and 18β-glycyrrhetic acid were kindly made available by Dr. S. Gottfried and the late Professor E. E. Turner, F.R.S. (Biorex Laboratories, London, E.C.1). A commercial sample of ammonium glycyrrhizate was obtained from L. Light & Co., Colnbrook, Bucks. Other derivatives of the glycyrrhetic acids and derivatives of oleanolic acid were synthesized as described below. Silica gel for column chromatography (type M.F.C.) was obtained from Hopkin and Williams, Chadwell Heath, Essex. Alumina (type H, P. Spence, Widnes, Lancs.) was deactivated with 10% of 10% (v/v) aqueous acetic acid.

METHODS

The purity of all compounds tested for uncoupling activity was checked by thin-layer chromatography on silica gel (Merck, Darmstadt; Grade H "nach Stahl") usually with ethyl acetate or ethyl acetate-light petroleum b.p. 60–80° (1:1 v/v) as the developing solvent. Compounds were visualized on the developed chromatoplates by one or more of the following procedures: spraying with water, exposure to iodine vapour; spraying with a 10% (w/v) solution of antimony trichloride in chloroform or glacial acetic acid, followed by heating at 105°; spraying with a 5% (w/v) solution of dodecamolybdophosphoric acid in ethanol and then heating at 80°. Ionophoresis on paper in aqueous or aqueous ethanolic buffers (containing up to 40% v/v ethanol) was also used to characterize triterpenoid acids; these were visualized by any of the above procedures or by inspection of dried ionophoretic strips under ultraviolet light.

Preparation of derivatives of glycyrrhetic acid (see Table 1 of Whitehouse, Dean & Halsall, 1967)

Methyl 3-O-(*β-carboxypropionyl*)-18α-*glycyrrhetate* (comp. 9 in the paper of Whitehouse & others 1967). A solution of 18α-glycyrrhetic acid (1 g) in methanol was treated with an excess of ethereal diazomethane solution. The mixture was acidified with acetic acid (0·5 ml) after 15 min and the ether evaporated off under reduced pressure. The white solid, methyl 18α-glycyrrhetate (1 g), which remained was dissolved in dry pyridine (20 ml) and the solution was treated with succinic anhydride (3 g). The mixture was heated under reflux for 8 hr.

The reaction mixture was cooled, poured into water (500 ml) and the precipitate filtered off, washed first with dilute hydrochloric acid, then with water, and then dried. Recrystallization from acetic acid-water gave methyl 3-*O*-(β-carboxypropionyl)-18α-glycyrrhetate as needles, m.p. 237–9° (Rf, 0·11; Rf, for methyl 18α-glycyrrhetate, 0·8) (Found: C, 71·15; H, 9·1; $C_{35}H_{52}O_7 + H_2O$ requires C, 70·8; H, 9·0%).

Methyl 3-O-(*β-carboxypropionyl*)-18β-*glycyrrhetate* (comp. 10). 18β-Glycyrrhetic acid was esterified with diazomethane as for 18α-acid and the resulting ester recrystallized from ethanol to yield plates, m.p. 253–4°.

A solution of the methyl 18β-glycyrrhetate (1 g) in pyridine (20 ml) was treated with succinic anhydride (0·5 g) and the mixture heated under

reflux for 12 hr. The reaction mixture was cooled and poured into water (20 ml). The suspension was extracted with ether (3 × 100 ml) and the ethereal extracts dried over magnesium sulphate. The solvents were evaporated leaving a white solid. Recrystallization from ethanol-water gave methyl 3-*O*-(β-carboxypropionyl)-18β-glycyrrhetate as plates, m.p. 265–7°; $[\alpha]_D + 70 \pm 1°$ (*c*, 1·05 in chloroform) (Found: C, 69·8; H, 8·9; $C_{35}H_{52}O_7 + H_2O$ requires C, 69·2; H, 9·0%).

3-O-*Acetyl*-18β-*glycyrrhetamide* (comp. 11). 18β-Glycyrrhetic acid was acetylated with acetic anhydride and pyridine. The product, 3-*O*-acetylglycyrrhetic acid, was recrystallized from ether to yield the acetate, m.p. 289–90°.

A solution of the acetylglycyrrhetic acid (1·6 g) in redistilled thionyl chloride (10 ml) was heated under reflux for 4 hr, while protected from atmospheric moisture with a calcium chloride tube. The excess of thionyl chloride was evaporated under reduced pressure and the remaining solid (acetylglycyrrhetyl chloride) was cooled and treated with strong ammonia solution (sp.gr. 0·88; 10 ml); a vigorous reaction took place and a white solid separated from the solution. The ammonia was evaporated and the aqueous suspension extracted with ether (3 × 50 ml). The combined ethereal extracts were dried over magnesium sulphate and the ether was evaporated. The product (1·6 g) was examined by thin-layer chromatography. Two spots were detected, Rf 0·63 and 0·25 (Rf, for acetylglycyrrhetic acid, 0·25). Recrystallization from ethanol gave 3-O-*acetyl*-18β-*glycyrrhetamide* as needles, m.p. 302–5° (Found: C, 74·6; H, 9·25; N, 2·4. $C_{32}H_{49}O_4N + H_2O$ requires C, 73·8; H, 9·7; N, 2·7%).

o-(3-O-*Acetyl*-18β-*glycyrrhetamido*)*benzoic* acid (comp. 22). 3-*O*-Acetyl-18β-glycyrrhetyl chloride (0·4 g) was added to a solution of anthranilic acid (0·3 g) in 10% sodium hydroxide solution (10 ml). The suspension was shaken at room temperature for ½ hr, the mixture acidified to litmus with dilute hydrochloric acid and extracted with ether. The ethereal extracts were dried over magnesium sulphate and the ether evaporated to give a brown solid (0·7 g). Recrystallization from methanol (twice) (charcoal) gave o-(3-O-*acetyl*-18β-*glycyrrhetamidobenzoic acid* as needles, m.p. 269° (decomp.). Rf, 0·05 (Rf for acetylglycyrrhetic acid, 0·25).

p-(3-O-*Acetyl*-18β-*glycyrrhetamido*)*benzoic acid* (comp. 23). 3-*O*-Acetyl-18β-glycyrrhetyl chloride (0·4 g) was added to a solution of *p*-aminobenzoic acid (0·3 g) in 10% sodium hydroxide solution (10 ml). The resulting suspension was acidified to litmus with dilute hydrochloric acid and extracted with ether-methanol (3:1 v/v) (3 × 100 ml). The extracts were combined and dried over magnesium sulphate. The solvents were evaporated to give a pale orange solid. Recrystallization from methanol gave *p*-(3-*O*-acetyl-18β-glycyrrhetamido)benzoic acid as needles, m.p. 260° (decomp.); Rf, 0·06 (Rf for acetylglycyrrhetic acid, 0·25).

3-O-(β-*Methoxycarbonylpropionyl*)*glycyrrhetic acid.* Succinic anhydride was converted into β-methoxycarbonylpropionyl chloride (Cason, 1955). It was obtained as a colourless liquid, b.p. 64–64·5°/1·7 mm.

A solution of glycyrrhetic acid (5·1 g) in pyridine (20 ml) was treated

with a solution of the β-methoxycarbonylpropionyl chloride (3 ml) in pyridine (50 ml). The reaction mixture was allowed to stand for 4 days. The solution was poured into water (100 ml) and extracted with ether (3 × 250 ml). The ethereal extracts were combined and dried over magnesium sulphate. The solvents were evaporated under reduced pressure to give a brown gum. 12-Fold fractional recrystallization from methanol-water gave 3-O-(*β-methoxycarbonylpropionyl)glycyrrhetic acid* as needles, m.p. 246–50° $[\alpha]_D$ + 74° ± 2° (*c*, 0·6 in chloroform) (Found: C, 71·6; H, 9·0; $C_{35}H_{52}O_7$ requires C, 71·9; H, 8·95%).

3-O-(*β-Methoxycarbonylpropionyl)glycyrrhetamide.* A solution of the 3-*O*-(β-methoxycarbonylpropionyl)glycyrrhetic acid (240 mg) in redistilled thionyl chloride (2 ml) was heated under reflux for 5 hr. Atmospheric moisture was excluded by using a calcium chloride tube. The excess of thionyl chloride was evaporated under reduced pressure, leaving a pale yellow solid. The solid was cooled and treated with strong ammonia solution (4 ml sp.gr. 0·88) and the reaction mixture was shaken for ½ hr at room temperature. The excess of ammonia was evaporated and the aqueous suspension extracted with ether (3 × 5 ml). The ethereal extracts were combined and dried over magnesium sulphate. The ether was evaporated leaving a pale yellow solid (200 mg). Recrystallization from methanol-acetone gave needles, m.p. 210–6°. The product was examined by thin-layer chromatography; two spots were detected, as having an Rf of 0·48 (principal component) and the other an Rf of 0·65 (Rf for 3-*O*-(β-methoxycarbonylpropionyl)glycyrrhetic acid, 0·66). Further recrystallization from methanol-acetone gave needles, m.p. 216–8°.

Hydrolysis of 3-O-(*β-methoxycarbonylpropionyl)glycyrrhetamide.* A solution of the ester (109 mg) in dimethylformamide (15 ml) was treated with anhydrous lithium iodide (1 g) and the solution heated under reflux for 12 hr (Dean, 1965). The reaction mixture was cooled and poured into water. The precipitate which formed was filtered off, washed with water and dried. Recrystallization from chloroform gave 3-*O*-(β-carboxypropionyl)glycyrrhetamide as plates, m.p. 247–50° (single spot on thin-layer chromatography).

9,11-Dehydro-11-deoxo-18β-glycyrrhetic acid (comp. 14). A solution of 18β-glycyrrhetic acid (3·9 g) in ethanol (100 ml) was treated with a solution of potassium borohydride (2 g) in water (10 ml). The mixture was heated under reflux for 1 hr, when a further quantity of potassium borohydride (2 g) was added to the reaction mixture, and the heating continued for 1 hr. The resulting solution was cooled and poured into dilute hydrochloric acid (about 100 ml). The suspension was extracted with ether (3 × 100 ml) and the ethereal extracts combined, washed with water and dried over magnesium sulphate. The ether was evaporated leaving a white solid, m.p. 284–6° (3·5 g). Examination by thin-layer chromatography showed the presence of three compounds with Rf 0·45, 0·35, 0·23 and with ultraviolet absorption maximum at 283 mμ, absent and 250 mμ respectively. The reaction product was adsorbed on silica gel (400 g) and successively eluted with light petroleum–benzene–ether. Elution with 20% ether–benzene gave crystalline fractions which showed

one spot when examined by thin-layer chromatography: Rf, 0·45, λ_{max} 283 mμ (ϵ, 10,000). Later fractions gave mixtures of two compounds with Rf, 0·45 and 0·23.

The yield of the combined diene fractions (λ_{max} 283 mμ) was 3 g. When this was recrystallized from methanol, 9,11-dehydro-11-deoxo-18β-glycyrrhetic acid was obtained as needles, m.p. 293–5°; λ_{max} 283 mμ (ϵ, 11,500) (Kurono (1938) gives m.p. 287° for this compound, prepared by sodium and ethanol reduction of glycyrrhetic acid).

3-O-(*β-Carboxypropionyl*)-9,11-*dehydro*-11-*deoxo*-18*β-glycyrrhetic acid* (comp. 15). A solution of 9,11-dehydro-11-deoxo-18β-glycyrrhetic acid (300 mg) in pyridine (10 ml) was treated with succinic anhydride (500 mg) and the mixture heated under reflux for 8 hr. The dark solution was cooled and poured into ice-dilute hydrochloric acid (approx. 30 ml). The product was extracted with ether (3 × 50 ml) and the ethereal extracts combined, washed with water (2 × 25 ml) and dried. Evaporation of the ether gave a solid (250 mg), which was recrystallized from acetic acid-ethanol-water (9 : 2 : 1 v/v) to give 3-O-(*β-carboxypropionyl*)-9,11-*dehydro*-11-*deoxo glycyrrhetic acid* as octahedra, m.p. 264–7°; $[\alpha]_D + 136 \pm 2°$ (*c*, 0·4 in chloroform); Rf, 0·1 (Rf, of starting material, 0·45).

11-*Deoxo*-18*β-glycyrrhetic acid* (comp. 12). A solution of 18β-glycyrrhetic acid (1·5 g) in glacial acetic acid (50 ml) was shaken with platinum oxide catalyst (0·5 g) for 7 hr under hydrogen at a pressure of 15 lb/in.^{2} The metallic suspension was filtered off and the filtrate evaporated to 30 ml under reduced pressure. 11-Deoxo-18β-glycyrrhetic acid crystallized as needles, m.p. 328–9°. The product had no ultraviolet absorption at 250 mμ and moved as a single spot on thin-layer chromatography; Rf, 0·6 (Rf for glycyrrhetic acid, 0·43; Rf of an authentic sample donated by the late Professor E. E. Turner, 0·6).

3-O-(*β-Carboxypropionyl*)-11-*deoxo*-18*β-glycyrrhetic acid* (comp. 13). A solution of 3-*O*-(β-carboxypropionyl)-18β-glycyrrhetic acid (455 mg) in acetic acid (18 ml) was shaken with platinum oxide catalyst (25 mg) in a hydrogen atmosphere as described. When the filtrate was evaporated to 5 ml, 3-O-(*β-carboxypropionyl*)-11-*deoxo*-18*β-glycyrrhetic acid* crystallized spontaneously as needles, m.p. 284–6° (Found: C, 72·3; H, 9·4. $C_{34}H_{52}O_6$ requires C, 73·2; H, 9·4%); $[\alpha]_D + 55° \pm 2°$ (*c*, 1·0 in ethanol). Only one component was detected by thin-layer chromatography Rf, 0·32 (Rf, for the starting material, 0·25). A solution of the product in ethanol had no ultraviolet absorption maximum at 250 mμ.

11-*Deoxo*-18*α-glycyrrhetic acid.* A solution of 18α-glycyrrhetic acid (383 mg) in dry dioxan (20 ml) was treated with platinum oxide catalyst (278 mg) suspended in acetic acid (20 ml). The hydrogenation was made as described above for 48 hr. The suspension was filtered and the filtrate was evaporated to dryness. The product was recrystallized from acetic acid to give impure 11-deoxo-18α-glycyrrhetic acid as needles, m.p. 288–92°. The ultraviolet absorption at 250 mμ of this product indicated that it also contained starting material (approx. 20% of which could not be separated by fractional recrystallization from acetic acid. [This mixture was examined for uncoupling activity].

N-(18β-*Glycyrrhetyl*)*glycine* ("Glycyrrhetinuric acid") (comp. 19). A solution of 18β-glycyrrhetic acid (4·7 g), freshly prepared ethyl glycine ester (1·0 ml) and dicyclohexylcarbodi-imide (2·06 g) in chloroform-methylene dichloride (1 : 1) (75 ml) was stirred at 25–30° for $\frac{1}{2}$ hr and at 20° for 48 hr. Acetic acid (5 drops) was added and the reaction mixture was filtered through sintered glass. The filtrate was diluted with chloroform and ether (total volume 100 ml) and passed down a column of alumina (B.D.H.). Elution with ether-chloroform (1 : 1) 500 ml gave two components, which were not glycyrrhetic acid, with Rf, 0·51 and 0·64 on thin-layer chromatography. (Rf for glycyrrhetic acid, 0·24 on the same plate).

The above solution was evaporated to dryness, the resulting solid was taken up in methanol (20 ml) and potassium hydroxide (0·6 g) was added. The solution was stirred at room temperature. After 2 hr, the solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate (3 × 50 ml). The combined ethyl acetate extracts were washed with water, dried over magnesium sulphate and the solvent evaporated.

The remaining solid was dissolved in ether and adsorbed on silica gel; elution with ether and ethyl acetate-ether 1 : 1 gave a single component when examined by thin-layer chromatography (Rf, 0·01) (Rf for glycyrrhetic acid, 0·20).

Evaporation of the solvents gave a colourless gum which was extracted with water, light petroleum (b.p. 60–80°) and ethyl acetate. About 80% was insoluble in water and light petroleum, but soluble in ethyl acetate. This portion was recrystallized from ethyl acetate-light petroleum to give needles, m.p. 264–4°. Recrystallization did not change the melting point. ν_{max} 2·92, 3·04, 5·87, 6·06, 6·21 μ (Nujol mull); (Found: C, 70·8; H, 9·1; N, 2·8. $C_{32}H_{49}O_5N + \frac{1}{2} H_2O$ requires C, 70·4; H, 9·4; N, 2·6%).

Preparation of derivatives of oleanolic acid

Methyl 3-O-*acetyl*-11-*oxo*-18β-*oleanolate*. This compound was prepared according to the method described by Bilham, Kon & Ross (1942). Rf, 0·79 (Rf for starting material, 0·85). The product was recrystallized from methanol-acetone to give methyl 3-*O*-acetyl-11-oxo-18β-oleanolate as needles, m.p. 240–1°; λ_{max} 250 mμ (ϵ, 10,960). [Bilham & others (1942) give 241–41·5°; λ_{max} 250 mμ (ϵ, 11,000)].

Hydrolysis of methyl 3-O-*acetyl*-11-*oxo*-18β-*oleanolate*. A solution of this ester (3·4 g) was partially hydrolysed with lithium iodide in 2,4,6-collidine (Elsinger, Schreiber & Eschenmoser, 1942). The product was recrystallized (charcoal) from methanol-chloroform to give 3-*O*-acetyl-11-oxo-18β-oleanolic acid as plates, m.p. 263–4° (the above authors give 264–5°).

The 3-*O*-acetyl group resisted (attempted) hydrolysis with 5% ethanolic potassium hydroxide solution under conditions which did not isomerize the D/E *cis*-ring junction.

11-*Oxo*-18α-oleanolic acid (comp. 29). A solution of 3-*O*-acetyl-11-oxo-18β-oleanolic acid (1 g) in ethanol (10 ml) was treated with potassium hydroxide (0·5 g). The mixture under nitrogen in the dark was heated under reflux for 3 hr and allowed to cool. The reaction mixture was

acidified with dilute sulphuric acid and extracted with chloroform (3 × 5 ml). The combined chloroform extracts were washed with water and dried over magnesium sulphate. The chloroform was then evaporated off and the colourless gum which remained was recrystallized from aqueous acetic acid to give 11-oxo-18α-oleanolic acid as plates m.p. 266–8° [Ruzicka & Cohen (1937) give 267–271°].

Methyl 3-O-(*β-methoxycarbonylpropionyl*)*oleanolate.* A solution of methyl oleanolate (5 g) in pyridine (50 ml) was treated with a solution of β-methoxycarbonylpropionyl chloride (3 ml) in pyridine (25 ml). The solution was shaken at room temperature for 48 hr. The reaction mixture was poured into water (100 ml) and extracted with ether (3 × 100 ml). The ethereal extracts were evaporated to dryness and the residue dried over concentrated sulphuric acid *in vacuo* for 48 hr. Recrystallization of the product (5·6 g) from methanol-ethyl acetate gave needles, m.p. 164–7°. The product gave a single spot on thin-layer chromatography: Rf, 0·74 (Rf, for methyl oleanolate, 0·65). Further recrystallizations gave *methyl* 3-O-(*β-methoxycarbonylpropionyl*)*oleanolate* as needles, m.p. 166–7°; $[\alpha]_D + 57° \pm 1°$ (*c*, 1·04 in chloroform) (Found: C, 73·7; H, 9·65; $C_{36}H_{56}O_6$ requires C, 74·0; H, 9·6%).

Methyl 3-O-(*β-methoxycarbonylpropionyl*)-11-*oxo*-18*β*-*oleanolate.* A solution of chromium trioxide (2·5 g) in 90% acetic acid (35 ml) was added dropwise over ½ hr to a solution of methyl 3-*O*-(β-methoxycarbonylpropionyl)-18β-oleanolate (2·6 g) in glacial acetic acid (23 ml). The mixture was then heated under reflux for 1·5 hr. Water (10 ml) was added and the solution left to cool. The white precipitate which formed was filtered off, washed with water and dried (2·1 g). The product was adsorbed on deactivated alumina (150 g) and eluted with light petroleum (b.p. 60–80°) –benzene–ether. The fractions eluted with benzene and ether showed one spot when examined by thin-layer chromatography; Rf, 0·63 (Rf for starting material, 0·74); λ_{max} 250 mμ; ν_{max} 1650cm^{-1}; the starting material did not absorb radiation at these frequencies. Recrystallization (three times) from methanol-water gave *methyl* 3-O-(*β-methoxycarbonylpropionyl*)-11-*oxo*-18*β*-*oleanolate* as needles, m.p. 193–193·5°; $[\alpha]_D + 66° \pm 2°$ (*c*, 0·87 in chloroform); λ_{max} 250 mμ, (ε, 11,000) (Found: C, 71·9; H, 8·9; $C_{36}H_{54}O_7$ requires C, 72·2; H, 9·0%). This compound gave no reaction with a Zimmermann reagent (2% ethanolic solution of *m*-dinitrobenzene mixed with 3·5N potassium hydroxide (1:1 v/v) (Corker, Norymbeski & Thow, 1962).

Hydrolysis of methyl 3-O-(*β-methoxycarbonylpropionyl*)-11-*oxo*-18*β*-*oleanolate.* This diester was hydrolysed by the following method of Dean (1965). A solution of the ester (212 mg) in dimethylformamide (10 ml) was treated with lithium iodide (*ca.* 1 g) and the solution heated under reflux for 22 hr. The reaction mixture was cooled and poured into water. The precipitate which was formed was filtered off, washed with water and dried. Recrystallization from acetic acid gave 3-O-(*β-carboxypropionyl*)-11-*oxo*-18*β*-*oleanolic acid* (comp. 31) as plates, m.p. 257–8° (one spot when analysed by thin-layer chromatography).

3-O-(*β-Carboxypropionyl*)-9,11-*dehydro*-18*β*-*oleanolic acid* (comp. 32).

A solution of 3-*O*-(β-carboxypropionyl)-18β-oleanolic acid (1·7 g) in carbon tetrachloride (30 ml) and light petroleum (b.p. 60–80°) (3·6 ml) was treated with *N*-bromosuccinimide (0·84 g). The reaction mixture was irradiated with a 250 W lamp for 7 min. During this period the solution was allowed to reflux. The reaction mixture was rapidly cooled and the unchanged succinimide was filtered off. Xylene (30 ml) and pyridine (10 ml) were added to the filtrate and the solution was evaporated at 90° to remove low-boiling solvents. A further quantity of pyridine (5 ml) was added. The solution was heated under reflux for 20 min and then filtered. Evaporation of the solvents under reduced pressure gave a yellow solid. Recrystallization from aqueous ethanol gave plates, m.p. 238–244°; recrystallization from acetic acid-water gave needles, m.p. 256–7°, λ_{max} 274 mμ (ε, 11,000).

Discussion

In instances where acid chlorides were required as intermediates in a synthetic sequence and where the ultimate product would probably have been water-insoluble, the protection of the 3β-hydroxyl group was achieved using the methylated half esters of succinic acid; the methyl ester could be selectively hydrolysed using lithium iodide in dimethylformamide without loss of the resulting hemisuccinate esters. The latter had a far greater degree of water solubility than the parent alcohol.

This procedure was also used before the oxidation of oleanolic acid.

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