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Preparation and characterization of the tropic acid esters of tropan-3β-ol, granatan-3α-ol and granatan-3β-ol

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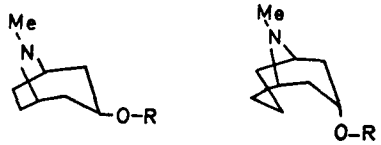
The preparation and characterization of the tropic acid esters of tropan-3β-ol and granatan-3α and 3β-ol are reported. A rapid synthesis of pseudopelletierine is described.

Reports of the mydriatic and spasmolytic activity of the tropate and mandelate esters of tropan-3β-ol, granatan-3α- and granatan-3β-ol are sparse and conflicting.



I II III

(a) R = CO·CH(CH$_2$OH)·Ph (tropate) (b) R = CO·CH(OH)·Ph (mandalate)

Although (±)-tropoyltropan-3β-ol (Ia) was initially reported to be devoid of mydriatic activity (Lieberman & Limpach, 1892), more recently Zipf, Dittman & Marquardt (1963) suggest a slight activity. [The report of mydriatic activity in (−)-Ia from *Dubiosia myoporoides* (Merck, 1892; Buanarotti, 1895) has been questioned (Carr & Reynolds, 1912), it being suggested that the compound isolated and tested was (−)-norhyoscyamine].

Early studies using the tropate and mandelate esters of the isomeric granatanols (IIa and b; IIIa and b) suggest that mydriatic activity resides in the β-isomers (IIIa and b) (Werner, 1918); the opposite conclusion has been drawn by Hartung & Gadekar (1953) employing only the mandelate esters.

In few of the above studies have the compounds been characterized: the present communication reports the preparation and characterization of (±)-tropoyl-tropan-3β-ol (Ia), (±)-tropoylgranatan-3α-ol (IIa) and (±)-tropoylgranatan-3β-ol (IIIa).

The preparation of pseudopelletierine by a Robinson-Schopf type of condensation under 'non-physiological' conditions has been carried out using the method of Elming (1960), Elming and Nedenskov (1958), Kay, Robinson & Thomas (1965).

Reduction of pseudopelletierine with (*a*) lithium aluminium hydride and (*b*) sodium in isobutanol gave granatan-3α-ol and granatan-3β-ol respectively (Chen & Le Fèvre, 1966).

The hydrochloride of the requisite amino-alcohol [tropan-3β-ol (I, R=H);

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granatan-3α-ol (II, R=H) and granatan-3β-ol (III, R=H)] was esterified with acetoxytropoyl chloride. Mild acid hydrolysis (5 min), followed by column chromatography of the basic material yielded the required product with the expected by products (I, II, III where R=H and R=CO·CH(CH_2OAc)·Ph). A third by-product was identified as the phenylacrylyl ester (I, II, III, R=CO·C(CH_2)·Ph). Such elimination of acetic acid is in line with earlier work (Garrett, 1957) and is supported by the solvent dependant nature of such reactions (Caldwell, Finkelstein & others, 1969).

EXPERIMENTAL

All melting points were recorded on a Kofler Hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 237 spectrophotometer and nmr spectra on a Varian HA-100 spectrometer using $CDCl_3$ solution and tetramethylsilane as standard. Mass spectra were recorded on an A.E.I. model MS9 spectrometer.

Pseudopelletierine (Elming, 1960). Acetonedicarboxylic acid (44·1 g; 0·3 mol), methylamine hydrochloride (20·25 g; 0·3 mol) and sodium acetate (92·5 g) in water (200 ml) was heated (90 min, 55–60°) with an aqueous solution of glutaraldehyde (28 ml; 25% w/v; 0·07 mol). After it had cooled, potassium carbonate (45 g) and sodium chloride (62·5 g) were added and the solution extracted with chloroform (10 × 200 ml). The combined chloroform extracts were dried ($MgSO_4$), filtered and the solvent removed. Distillation of the brown viscous residue gave pseudopelletierine (5·5 g) $b.p._{.13}$ 129–130° as a colourless liquid which rapidly solidified m.p. 47–48° (Lit m.p. 48° [Putney & Soine, 1955]). ν_{max} (Nujol) 1720 cm^{-1} (C=O), τ($CDCl_3$) 6·8 (2H, m, C–1H, C–5H), 7·45 (3H, s, N–CH_3), 7·15–8·7 (10H, m, methylene groups).

Granatan-3β-ol. Reduction of pseudopelletierine (6 g) using the method of Nickon & Fieser (1952) gave granatan-3β-ol (3·8 g) $b.p._{.18}$ 141–142° crystallizing from benzene–light petroleum (b.p. 40–60°) m.p. 100° (Lit m.p. 96° [Hartung & Gadekar, 1953], ν_{max} (Nujol) 3400 cm^{-1} (broad) (bonded-OH), τ($CDCl_3$) 5·6 broad (1H, m, C–3H; $W_{1/2}$ = 16 Hz), 7·05 (2H, m, C–1H, C–5H), 7·5 (3H, s, N–CH_3), 7·8–8·7 (10H, m, methylene groups) 7·3 (1H, s, disappears on deuteration).

Granatan-3α-ol synthesized by the method of Chen & Le Fevre (1966) had the following characteristics: $b.p._{.13}$ = 138–140°, m.p. 63–64°. ν_{max} (Nujol) 3400 cm^{-1} (broad) (–OH), τ($CDCl_3$) 5·8 (1H, m, C–3H; $W_{1/2}$ = 12·5 Hz), 6·8–7·2 (3H, m, C–1H, C–5H, and OH) (collapses to 2H multiplet on adding D_2O), 7·54 (3H, s, N–CH_3), 7·4–9·0 (10H, m, methylene groups).

Tropoyltropan-3β-ol. Pseudotropine hydrochloride (2 g) (Nickon & Fieser, 1952) and acetyltropoyl chloride (3·5 g) (Wolfenstein & Mamlock, 1908) were heated (4 h: 100°), with occasional swirling. After cooling, water (30 ml) was added and the mixture heated (5 min, 100°) then rapidly cooled and immediately extracted with ether (3 × 50 ml) and the ether rejected. The aqueous solution was basified (K_2CO_3) and extracted with ether (6 × 50 ml) then with chloroform (3 × 50 ml). The combined extracts were dried ($MgSO_4$), filtered and the solvents removed to leave an oily residue which was dissolved in the minimum quantity of chloroform–ether (3:7 parts v/v) and added to a column of alumina (2·5 × 50 cm; Laporte Type H; 100–200 mesh). The column was eluted with chloroform–ether (3:7 parts by volume) (700 ml) then with chloroform–ether (3:7 parts by volume) containing (*a*) 2% ethanol

(300 ml); (*b*) 4% ethanol (300 ml); (*c*) 6% ethanol (300 ml); (*d*) 8% ethanol (300 ml); (*e*) 10% ethanol (300 ml). Fractions each of 25 ml were collected and monitored via the infrared spectrum of the residue after removal of the solvent. Four components (A–D) were isolated and identified in the eluate.

Component A (fractions 3–4): a colourless oil identified as 2-phenylacrylyltropan-3β-ol (atropoyltropan-3β-ol). ν_{max} (liquid film), 1730 cm^{-1} (C=O), 1630 cm^{-1} (C=C stretch), 1605, 1580, 1500 cm^{-1} (aromatic C=C in plane vibrations). $\tau(CDCl_3)$ 2·8 (5H, m, aromatic), 3·75, 4·15 (2H, d, [J = 2 Hz] olefinic protons), 4·85 (1H, m, C–3H), 6·8 (2H, m, C–1H, C–5H), 7·7 (3H, s, N–CH_3), 7·8–8·45 (8H, m, methylene groups). Molecular weight (mass spectrum) m/e = 271; $C_{17}H_{21}NO_2$ requires mol. wt = 271.

Component B (fractions 6–16): a colourless oil, identified as acetyltropoyltropan-3β-ol ν_{max} (liquid film), 1730, 1750 cm^{-1} (C=O), 1605, 1580, 1500 cm^{-1} (aromatic). $\tau(CDCl_3)$ 2·7 (5H, m, aromatic), 5·0 (1H, m, C–3H), 6·0–6·3 (3H, m, –CH·CH_2O), 6·8 (2H, m, C–1H, C–5H), 7·7 (3H, s, N–CH_3), 8·0 (3H, s, O·$COCH_3$), 8·1–8·5 (8H, m, methylene groups).

Component C (fractions 29–62): tropoyltropan-3β-ol (190 mg) was obtained as an oil which slowly crystallized on standing. ν_{max} (liquid film), 1740 cm^{-1} (C=O), 1605, 1580, 1500 (aromatic), 3400 cm^{-1} (broad) (bonded –OH). $\tau(CDCl_3)$ 2·75 (5H, s, aromatic), 4·95 (1H, m, C–3H) ($W_{1/2}$ = 17 Hz), 5·9–6·2 (3H, m, –CH–CH_2–O), 6·8 (2H, m, C–1H, C–5H), 7·7 (3H, s, N–CH_3), 7·9–8·5 (8H, m, methylene groups), 7·8 (1H, s, –OH) (disappears on deuteration). Molecular weight (mass spectrum) m/e = 289: $C_{17}H_{23}NO_3$ requires mol. wt = 289.

Hydrobromide, m.p. 168–169°. Found: C, 55·0; H, 6·7; N, 3·8. $C_{17}H_{24}Br.NO_3$ requires C, 55·1; H, 6·5; N, 3·8%.

Component D (fractions 65–74): colourless needles of pseudotropine m.p. 103–105°.

Fractions 5–16 were combined, and acidified to pH 3 with N/100 HCl. The solution was heated on a steam bath for 30 min, cooled and the basic products extracted. Column chromatography of the material under the same conditions as previously described gave a further quantity of tropoyltropan-3β-ol (130 mg) in fractions 29–54.

Tropoylgranatan-3β-ol was prepared as above by heating (2 h) granatan-3β-ol hydrochloride (2·5 g) and acetyltropoyl chloride (4 g). The basic product of the reaction in chloroform–ether (1 : 1 parts by volume) was added to an alumina column (2·5 × 50 cm; Type H, 100–200 mesh). Elution with chloroform–ether (1 : 1 parts by volume, 700 ml) followed by chloroform–ether (1 : 1) (300 ml) containing (*a*) 2% ethanol; (*b*) 4% ethanol; (*c*) 6% ethanol; (*d*) 8% ethanol; (*e*) 10% ethanol. Fractions each of 25 ml were collected and examined as before when the four components below, resulted.

Component A (fractions 4–6): a colourless oil (0·8 g) identified as atropoylgranatan-3β-ol. ν_{max} (liquid film), 1730 cm^{-1} (C=O), 1630 cm^{-1} (C=C stretch), 1610, 1590, 1505 (aromatic in plane vibrations). $\tau(CDCl_3)$ 2·075 (5H, m, aromatic), 3·7, 4·15 (2H, d, [J = 2 Hz], =CH_2), 4·25 (1H, m, C–3H), 7·05 (2H, m, C–1H, C–5H), 7·5 (3H, s, N–CH_3), 7·9–8·6 (10H, m, methylene groups); molecular weight (mass spectrum) m/e = 285; $C_{18}H_{23}NO_2$ requires mol. wt = 285.

Component B (fractions 7–20): a colourless oil, identified as acetyltropoylgranatan-3β-ol. ν_{max} (liquid film), 1745, 1720 cm^{-1} (C=O), 1600, 1580, 1500 cm^{-1} (aromatic).

$\tau(CDCl_3)$ 2·7 (5H, s, aromatic H), 4·4 (1H, m, C–3H), 6·0 (3H, m, $-CH\cdot CH_2$), 7·05 (2H, m, C–1H, C–5H), 7·5 (3H, s, $N-CH_3$), 7·95 (3H, s, –O, $CO\cdot CH_3$), 8·0–8·6 (10H, m, methylene groups).

Component C (fractions 29–36): a colourless oil (460 mg) identified as tropoylgranatan-3β-ol. ν_{max} (liquid film), 3420 cm^{-1} (broad, bonded –OH), 1720 cm^{-1} (C=O), 1600, 1580, 1500 cm^{-1} (aromatic in plane vibrations). $\tau(CDCl_3)$ 2·5 (5H, s, aromatic), 4·45 (1H, m, C–3H), 5·9–6·2 (3H, m, $-CH\cdot CH_2$), 7·1 (2H, m, C–1H, C–5H), 7·5 (1H, s, disappears on deuteration, –OH), 7·6 (3H, s, $N-CH_3$), 8·0–8·8 (10H, m, methylene groups). Molecular weight (mass spectrum) m/e = 303; $C_{18}H_{25}NO_3$ requires mol. wt = 303.

Hydrobromide, m.p. 168–169°. Found C, 56·3; H, 6·6; N, 3·4. $C_{18}H_{26}Br.NO_3$ requires C, 56·3; H, 6·8; N, 3·6%.

Component D (fractions 39–46): a colourless crystalline produce identified as granatan-3β-ol, m.p. 97–98°.

Tropoylgranatan-3α-ol was prepared as above by heating (3 h, 100°) granatan-3α-ol hydrochloride (2·6 g) and acetyltropoyl chloride (3·75 g). The basic reaction product in chloroform–ether (2:1 parts by volume) was added to the alumina column and eluted with chloroform–ether (2:1 parts by volume, 700 ml) followed by chloroform–ether (2:1) (300 ml) containing (*a*) 2% ethanol; (*b*) 4% ethanol; (*c*) 6% ethanol; (*d*) 8% ethanol; (*e*) 10% ethanol.

Fractions each of 25 ml were collected and examined as before when four components were isolated.

Component A (fractions 16–19): a colourless oil (0·9 g) identified as atropoylgranatan-3α-ol. ν_{max} (liquid film), 1725 cm^{-1} (C=O), 1630 cm^{-1} (C=C stretch), 1610, 1590, 1505 cm^{-1} (aromatic C=C in plane vibrations). $\tau(CDCl_3)$ 2·5 (5H, m, aromatic), 3·8–4·15 (2H, d, [J = 1 Hz], $=CH_2$), 4·7 (1H, m, C–3H), 7·15 (2H, m, C–1H, C–5H), 7·55 (3H, s, $N-CH_3$), 7·9–8·9 (10H, m, methylene groups). Molecular weight (mass spectrum) m/e = 283.

Component B (fractions 21–29): a colourless oil, identified as acetyltropoylgranatan-3α-ol. ν_{max} (liquid film), 1730, 1750 cm^{-1} (C=O), 1600, 1590, 1500 cm^{-1} (aromatic).

Component C (fractions 40–44) contained two components, but was predominantly granatan-3α-ol.

Component D (fractions 45–70): a colourless oil (0·3 g), tropoylgranatan-3α-ol, ν_{max} (liquid film), 3400 cm^{-1} (broad, bonded –OH), 1740 cm^{-1} (C=O), 1610, 1600, 1505 cm^{-1} (aromatic). $\tau(CDCl_3)$ 2·75 (5H, s, aromatic), 4·85 (1H, m, C–3H), 5·85–6·2 (3H, m, $-CH\cdot CH_2$), 7·1 (2H, m, C–1H, C–5H), 7·6 (3H, s, $N-CH_3$), 7·9 (1H, s, disappears on deuteration), 7·7–9 (10H, m, methylene groups). Molecular weight (mass spectrum), m/e = 303.

Hydrobromide, m.p. 183–184°. Found C, 56·2; H, 6·6; N, 3·1%.

A further quantity of tropoylgranatan-3α-ol (0·16 g) was obtained by repeating the selective hydrolysis, and purification on component B.

Hydrobromide salts of tropate esters. The isolated tropate esters were dissolved in dry ether and dry HBr gas bubbled through the solution. The precipitate was collected, dried and recrystallized to constant m.p. from ethanol ether mixture.

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