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6β-PROPANOYLOXY-3α-TIGLOYLOXYTROPANE, A NEW ALKALOID FROM *DATURA INNOXIA*

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Abstract—A new alkaloid, shown by spectroscopic and degradative means to be 6β-propanoyloxy-3α-tigloyloxytropane has been isolated from *Datura innoxia* root. The synthesis of the natural and (±) base is described.

Datura innoxia Miller (Solanaceae) is a herbaceous white flowered annual which is classified along with the closely similar *D. meteloides* DC ex Dunal in Section Dutra of the genus.[1] It has been extensively investigated in the past and has been the source of several new tigloyl esters.[2,3] During routine analysis of the root for 3α,6β-ditigloyloxytropane and 3α,6β-ditigloyloxytropan-7β-ol using the modified[3] Evans and Partridge system,[4] a small shoulder on the elution curve was noticed on the down-side of the 3α,6β-ditigloyloxytropane peak. Although present in only a small quantity (0·003%) the new base, $[\alpha]_D^{23} = 0°$, picrate m.p. 163° was isolated by bulking together material from several columns. The base $C_{16}H_{25}NO_4$ (MS) had M = 295 (6%) and a fragmentation pattern characteristic of the tropane nucleus.[5] Since the base peak was at $m/e = 94$ it was assumed that the alkaloid was a dihydroxytropane derivative, and the peak at $M^+ - 99$ was tentatively assigned to the loss of a tigloyl residue. The IR showed two ester carbonyl bands at 1740 and 1708 cm^{-1} (unsat.), and $>C=C<$ at 1630 cm^{-1}. Examination of the NMR spectrum (in $CDCl_3$ using TMS as internal standard) confirmed the presence of a di-substituted tropane nucleus with one tigloyl group,[6,7] and showed the following signals: $\tau = 4{\cdot}49$ (*dd* due to the tropane C(6) proton coupling with the C(7) α and β protons); 4·89 (*t* tropane 3β proton) thus indicating the α orientation for the C(3) acyl group;[8] 6·76 [*bm* tropane C(1) and (5)]; 7·43 (*s N*-Me); 3·10 (*q* tigloyl 3β proton coupling with the β methyl); 8·13 (*s* tigloyl α methyl); 8·17 (*d* tigloyl β methyl partly overshadowed by the signal at $\tau = 8{\cdot}13$). In addition signals at $=7{\cdot}67$ (*q* $MeCH_2$) and 8·86 (*t* CH_3CH_2) suggested that the base was probably a propanoyl ester. Hydrolysis of the base gave two acids, propanoic and tiglic, identified by GLC and in the case of tiglic acid m.p. and m.m.p. The alkamine was esterified

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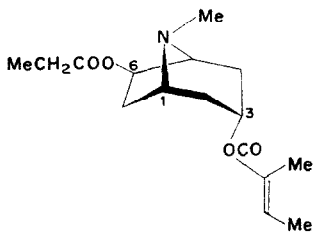
with tigloyl chloride and gave (−)-3α,6β-ditigloyloxytropane thereby indicating that it was (+)-tropan-3α,6β-diol which is known to have the 3R 6R configuration[9] (structure).



6β-Propanoyloxy-3α-tigloyloxytropane.

The relative positions of the tigloyl and propanoyl moieties were determined in two ways. Partial hydrolysis[10,11] of (−)-3α,6β-ditigloyloxytropane gave (−)-6β-hydroxy-3α-tigloyloxytropane in 34% yield. Esterification of the latter base with propanoyl chloride gave a product indistinguishable from the natural base (slightly higher picrate m.p.). Secondly, (±)-6β-hydroxytropan-3-one was esterified with propanoyl chloride and reduced to the 3α-ol using Raney nickel. The 3α-tigloyl ester had NMR, MS and IR spectra and R_f values on TLC and partition columns very similar to the natural alkaloid.

The appearance of a propanoyl ester in the Solanaceae tropane series seems to be unique, although 3α-propanoyloxytropane has been isolated from *Bruguiera sexangula* and *B. exaristata* (Rhizophoraceae).[12] Similarly, the hetero di-esters of dihydroxytropane are extremely rare, 6β-acetoxy-3α-tigloyloxytropane and 6β-(2-methylbutanoyloxy)-3α-tigloyloxytropane occurring in *D. sanguinea* R. and P.,[6] and *D. suaveolens* H. and B. ex Willd., respectively.[13] Both these plants are in Section Brugmansia (perennial tree-daturas), a group quite different from the more common herbaceous daturas with perhaps the exception of *D. ceratocaula* Ort. The dextrorotatory enantiomer of dihydroxytropane appears to be a characteristic of the genus as a whole but (−)-tropan-3α,6β-diol (valerine) occurs only in Duboisia[14] as the alkamine of the alkaloid valeriodine.

EXPERIMENTAL

Optical rotations were measured using a Bendix NPL automatic polarimeter type 143. *Datura innoxia* plants were grown on open land in the University of Nottingham and were of the same strain (English sample) examined previously.[3]

Isolation of alkaloids. Dried, finely powered *D. innoxia* root (50 g) was mixed with 12·5 g $Ca(OH)_2$, moistened with H_2O (*ca* 25 ml) and exhaustively extracted with Et_2O. After removal of the solvent, the residue in $CHCl_3$ (*ca* 2 ml) was transferred to a kieselguhr column (10 g) supporting 0·5 M phosphate buffer pH 6·8 (5 ml). Elution with petrol. (100 ml) gave a mixture of bases which was further resolved on a kieselguhr column (10 g) containing 5 ml 0·5 M phosphate buffer pH 5·6. The elution curve (titre, ml 0·005 N H_2SO_4 using bromocresol green indicator vs fraction (5 ml) number) showed three peaks designated *A*, *B* and *C*: in petrol. b.p. 40–60, *A* (sharp) 24 mg; *B* (shoulder) 1·8 mg; in Et_2O, *C* (sharp) 10·1 mg. TLC Alumina (Merck), Et_2O, detected with I_2/CCl_4 suggested that *A* and *C* were 3α,6β-ditigloyloxytropane and 3α,6β-ditigloyloxytropan-7β-ol respectively. These bases were characterized as the picrates[2] (m.p., m.m.p. and IR). The separation was repeated several times in order to isolate sufficient *B*. Base *B*, colourless gum, $[\alpha]_D^{23} = 0°$ (undetectable). Picrate recryst. from $EtOH/H_2O$ m.p. 163° (needles); IR ν_{max}^{KBr} 1740, 1708, 1630, 1560, 1485, 1430, 1365, 1318, 1245, 1150, 1065, 907, 780, 735, 705

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cm^{-1}; MS *m/e* with *I* % in parentheses, 42 (23), 55 (26), 57 (16), 81 (13), 82 (10), 83 (20), 94 (100), 95 (95), 96 (14), 122 (39), 138 (19), 195 (8), 196 (11), M^+ = 295 (6). Accurate mass measurement, M^+ = 295·1787, $C_{16}H_{25}NO_4$ requires 295·1784. NMR (base regenerated from the picrate in $CDCl_3$ using TMS as internal standard), τ = 3·10 (1H *q J* 7 Hz), 4·49 (1H *dd J* 3 and 5 Hz), 4·89 (1H *t J* 4 Hz), 6·76 (*bm*), 7·43 (3H *s*), 7·67 (2H *q J* 8 Hz), 8·13 (3H *s*), 8·17 (3H *d J* 4 Hz), 8·86 (3H *t J* 7 Hz).

Hydrolysis of base. The base (4·5 mg) was heated at 100° in a sealed tube with 5% $Ba(OH)_2$ (7 ml) for 2 hr. Cooled hydrolysate was acidified (80% H_2SO_4) and extracted with Et_2O (4 × 10 ml). The remaining aqu. phase was neutralized (solid $BaCO_3$), centrifuged and the supernatant liquid and washings were evaporated to dryness under reduced pressure. The dried residue was then heated under reflux with tigloyl chloride (0·2 ml) for 3 hr,[14] cooled, washed several times with Et_2O, basified, and extracted with $CHCl_3$. Evaluation of the product by TLC (Alumina, Et_2O) showed only one spot with an R_f identical to that of 3α,6β-ditigloyloxytropane. The picrate (yield 2 mg) had m.p. and m.m.p. and IR identical to authentic (−)-3α,6β-ditigloyloxytropane picrate, and the base recovered from the picrate had $[\alpha]_D^{21}$ = −18·46° c.f. −18·82° determined on the authentic base under the same conditions. The Et_2O extract of the acidified hydrolysate was examined by GLC on a 3 ft celite column containing 10% silicone oil and 2% orthophosphoric acid; *N* flow rate 30 ml/min, F.I. detector with temp. programme 30–160° (32°/min).[b] After GLC, the Et_2O was allowed to evaporate and this deposited a few crystals of tiglic acid m.p. 62°.

Partial synthesis of 6β-propanoyloxy-3α-tigloyloxytropane. (−)-3α,6β-Ditigloyloxytropane (58 mg) in Me_2CO (1·5 ml) and 0·1 N NaOH 2·7 ml maintained at 22° for 4 hr, and then neutralized with HCl (10%). The Me_2CO was removed *in vacuo* and the remaining basified (NH_4OH) solution extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave an oily straw-coloured residue which was resolved on a partition column at pH 6·8. Elution with petrol. (75 ml) gave unchanged starting material, Et_2O (75 ml) gave 6β-tigloyloxytropan-3α-ol[11] and $CHCl_3$ gave (−)-6β-hydroxy-3α-tigloyloxytropane (14·8 mg), which was dried and heated under reflux (80–85°) with propanoyl chloride (0·2 ml), for 2 hr. The product was purified by partition column chromatography at pH 6·8 (yield 10 mg) $[\alpha]_D^{23}$ = 0°, NMR identical with natural base, picrate m.p. 168°.

(±)-6β-*Propanoyloxy-3α-tigloyloxytropane.* Dry 6β-hydroxytropan-3-one (25 mg) was esterified with propanoyl chloride (0·5 ml) and the recovered base in EtOH reduced (at. press.) with H_2 in the presence of Raney Ni. The product (TLC pure 6β-propanoyloxytropan-3α-ol R_f 0·59 Alumina Et_2O:EtOH 4:1) was not isolated but esterified with tigloyl chloride and purified by the method outlined above to give (±)-6β-propanoyloxy-3α-tigloyloxytropane, NMR identical to natural base, picrate m.p. 169°.

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