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ANGELOYL CHLORIDE: SYNTHESIS AND UTILISATION IN THE PARTIAL SYNTHESIS OF LANTADENE A (REHMANNIC ACID)

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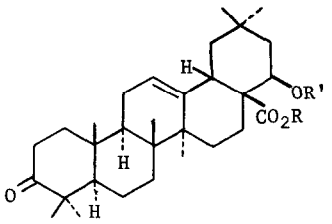
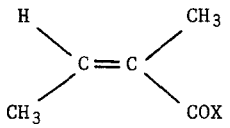
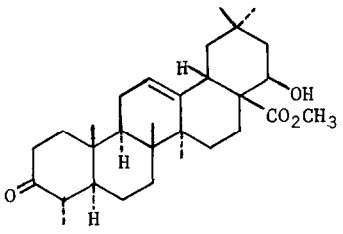
Our interest in preparing partially-synthetic analogues of the hepatotoxic triterpene lantadene A[1] (1) led us to re-examine the question of whether angeloyl chloride (2) can be prepared and used in the synthesis of angelate esters of complex alcohols. We now report the synthesis of angeloyl chloride (2), and the partial synthesis of lantadene A (1).





1 R = H, R' = angeloyl
6 R = R' = H
7 R = $CH\emptyset_2$, R' = H
8 R = $CH\emptyset_2$, R' = angeloyl
9 R = $CH\emptyset_2$, R' = tigloyl

2 X = Cl
3 X = OH
4 X = O^-K^+



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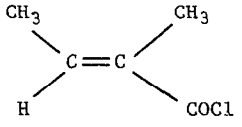

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It is surprising that although angelic acid has been known for 130 years, an unambiguous synthesis of the derived acid chloride has not yet been described. Rupe[2] in 1909 made the first claim for the synthesis of angeloyl chloride (2) by treating sodium angelate with $POCl_3$. However, Kupchan and Afonso[3] on repeating this work were only able to obtain tigloyl chloride (5). They also reported unsuccessful attempts to convert 3 into 2 using PCl_3 and $SOCl_2$. More recently Olah et al[4] described an unsuccessful attempt at converting 3 into 2 using $SOCl_2$. Kupchan[3,6] has described a method for preparing angelate esters which involves esterification with 3-bromoangeloyl chloride and hydrogenolysis over Pd/C of the resulting 3-bromoangelate ester. However, in applying this method others[7] encountered both isomerisation and over-reduction.

We were encouraged by a report by Bohlmann and Tietze[5] who described the preparation of an acid chloride by treating angelic acid (3) with oxalyl chloride. The acid chloride was reacted with an alcohol to give the corresponding angelate and tiglate esters in ca 2:1 ratio.

We reasoned that the synthesis of 2 might be possible if a method avoiding heat and strong acids or bases was used. A fine suspension of the dry potassium salt (4)[8] (0.5g) in dry ether (10ml) was stirred at 0° under N_2 and oxalyl chloride (2ml) and a drop of DMF were added. After stirring for 2 hr at 0° the mixture was filtered and the filtrate concentrated on the rotary evaporator using only a slight vacuum at room temperature. CCl_4 was added to the residue and the concentration repeated to ensure removal of excess oxalyl chloride. The resulting pale yellow oil (0.4g) was essentially pure[9] angeloyl chloride (2) as judged by nmr ($CDCl_3$), which showed the vinylic proton as a multiplet at δ6.25 (the corresponding proton in 5 appears as a multiplet at δ7.35).

In attempting a partial synthesis of lantadene A, we chose as starting material the ester (7) in which the carboxyl group is protected as the benzhydryl ester. The ester (7), mp 233-235°, $[\alpha]_D$ + 61° (C=1, $CHCl_3$), was readily prepared by treatment of the acid (6)[1b] with diphenyldiazomethane. The ester (7) (0.4g) in THF (5ml) was treated with angeloyl chloride (2) (from 4, 1g) at room temperature for 2 days and chromatography of the produce on silica gel gave 0.18g (40%) of the ester (8) as a colourless oil, $[\alpha]_D$ + 48° (C=1.8, $CHCl_3$), nmr ($CDCl_3$) δ5.86 (m, 1H, angelate vinylic), and unreacted 7 (0.2g). None of the tiglate ester (9) was

detected by nmr. The product (8) was identical (TLC, nmr) with material obtained by treating lantadene A (1) with diphenyldiazomethane. The benzhydryl protecting group of 8 was cleaved with trifluoroacetic acid and anisole at 0° for 5 min, and the resulting crude acid recrystallised from methanol to give lantadene A, mp 285-290° (lit[1a] 282-286°), indentical in all respects with authentic lantadene A.

Conversely, when the ester (7) (0.2g) in pyridine solution (3ml) was treated with angeloyl chloride (from 4, 0.4g) at room temperature overnight, a compound (50mg, 22%) with the same TLC mobility as 8 was isolated as an oil, $[\alpha]_D$ + 41° (C=1.2, $CHCl_3$). The nmr ($CDCl_3$) showed this to be entirely the tiglate ester (9) (δ6.50, m, 1H, tiglate vinylic). The same compound was obtained in 45% yield by overnight treatment of 7 in pyridine with tigloyl chloride (5). We only obtained traces of 9 when the reaction was carried out in THF solution.

The obvious crowding around the axial hydroxyl group makes 7 a difficult model compound for an acylation reaction. Barton and de Mayo[10] noted that the related alcohol (10) was resistant to acetylation. The success in our case suggests that this method should be readily applicable to other alcohols[12].

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