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SYNTHESIS OF A TRANSITION STATE ANALOGUE FOR THE HYDROLYSIS OF COCAINE: ASSISTANCE TO PHOSPHONYLATION OF A 3β-HYDROXYTROPANE BY A NEIGHBOURING AMIDE GROUP.

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Abstract: A simple synthesis of phenylphosphonate monoester analogues of the transition state for hydrolysis of the benzoyl ester group in cocaine is provided by the reaction of 2β-amido-3β-tropanols with phenylphosphonyl dichloride. Steric hindrance to phosphonylation of the hydroxyl is overcome because the neighbouring 2β-amido group participates in the reaction. The intramolecular assistance by the amide to formation of the phosphonate ester is influenced by the electronic environment of the amide group.

There is considerable current interest[1-6] in the synthesis of phenylphosphonate monoesters of general structure **1** as transition state analogues for the generation of antibodies that will catalyse the hydrolysis of cocaine **2**. In syntheses described to-date, obstacles have been encountered in phosphonylating the 3β-hydroxyl group of precursor ecgonine derivatives such as **3** to give the required phenylphosphonate esters. It is assumed that the hydroxyl is sterically hindered,[1] although electronic effects may also be important.[6] We herein report a facile synthesis of related phenylphosphonate monoester transition state analogues which is made possible because the amide group in 2β-amido-3β-tropanols such as **4** participates in the phenylphosphonyl dichloride mediated phosphonylation of the hydroxyl group.

The first synthesis[1] of phenylphosphonate monoester analogues of cocaine overcame the difficulties described above by developing a new method[7] for the preparation of phenylphosphonate monoesters from hindered alcohols. More recently, Cashman's group reported[6] that all attempts to phenylphosphonylate the ecgonine amide **3** failed, and the desired phenylphosphonate monoester was synthesised from norecgonine **5** by a multi step procedure where success crucially depended upon protection of the bridgehead nitrogen as the O-benzyl carbamate prior to phenylphosphonylation of the hydroxyl group (by using the above procedure[7]). N-deprotection followed by N-methylation was then necessary.

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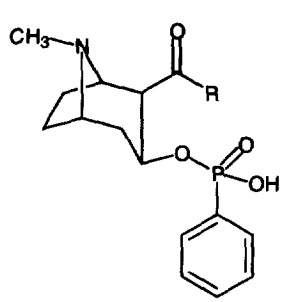

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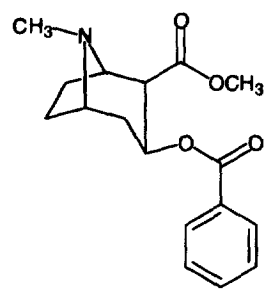

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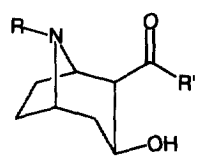
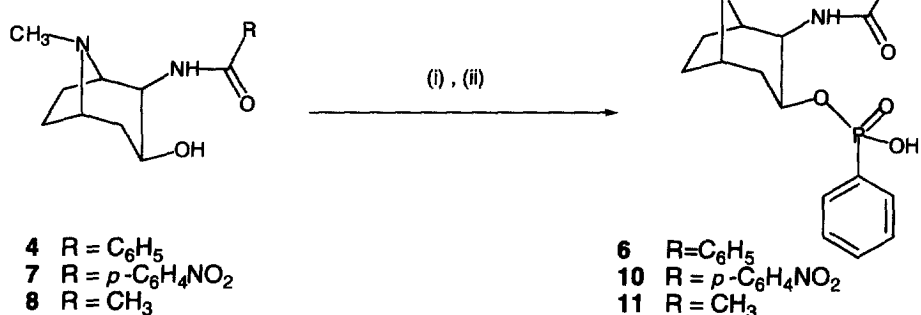


3 R = CH_3, R' = $NH(CH_2)_5CO_2CH_3$
5 R = H, R' = OH

Cashman's report prompts us to describe our own results for the synthesis of related phenylphosphonate monoesters from amido substituted tropanols. Reaction of 2β-benzamido-3β-tropanol **4**[8] with phenylphosphonyl dichloride ($PhPOCl_2$, anhydrous pyridine, RT, N_2 atmosphere, 3d) followed by hydrolysis *in situ* (H_2O, 2h) gave the phenylphosphonate monoester **6** in 40% overall yield.



4 R = C_6H_5
7 R = *p*-$C_6H_4NO_2$
8 R = CH_3
9 R = $CH_2CH_2CH_2CH_2CH_2NO_2$

6 R=C_6H_5
10 R = *p*-$C_6H_4NO_2$
11 R = CH_3
12 R = $CH_2CH_2CH_2CH_2CH_2NO_2$

Scheme 1: Synthesis of phenylphosphonate analogues, (i) $PhPOCl_2$, anhydrous pyridine, 25°C, nitrogen atmosphere (ii) H_2O, pyridine, 25°C

It is remarkable that the benzamidotropanol **4** reacts with phenylphosphonyl dichloride whereas the carboxyamidotropanol **3** and analogous ecgonine esters do not (this lack of reactivity was also found in our

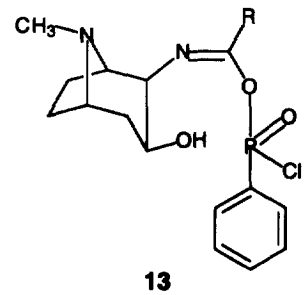
laboratories). To further explore the successful phosphonylation reaction (and to provide compounds for the generation of catalytic antibodies) the amidotropanols **7** - **9** (obtained by acylation of 2β-amino-3β-tropinol[8] with the appropriate acid chloride) were reacted with phenylphosphonyl dichloride and water as described above (except that longer reaction times were required). The corresponding phenylphosphonate half esters **10** - **12** were obtained and reaction times and overall yields are summarised in Table 1.

Table 1. The reactions of amidotropanols **4**, **7**, **8**, and **9** with phenylphosphonyl dichloride

Starting Material	Product	Reaction Time (days)	% Yield[a]
4	**6**	3	40
7	**10**	4	34
8	**11**	5	8
9	**12**	5	10

a - In each case the phosphonylation was followed by a 2h hydrolysis and the yield shown is for the reaction overall and is based on the starting amidotropanol.

These results show that the phosphonylation reaction is sensitive to the nature of the amide substituent adjacent to the reacting hydroxyl. The sterically least demanding amide substituent, the acetamide **8**, requires the longest reaction time and gives the lowest yield. It may be concluded, therefore, that the different reactivities of the amidotropanols **4** and **7** - **9** in the phosphonylation reaction are not the result of simple steric effects. The reactions of the benzamidotropanol **4** and the nitrobenzamidotropanol **7** are highly revealing. Benzamidotropanol **4** requires the shortest reaction time and gives the highest yield. Introduction of the electron withdrawing nitro substituent lowers the yield and necessitates an increased reaction time. The reactivity effects, therefore, have an electronic component. The simplest explanation of these observations would invoke participation of the adjacent amide group which reacts with the phenylphosphonyl dichloride to form an intermediate such as the imino phosphonate **13**. Intramolecular transfer, either directly (*via* a seven membered cyclic transition state) or indirectly (by O-N migration followed by the generation of a five membered ring), then allows formation of the required phosphonate ester bond. This explanation would account for the increased reactivity of the arylamidotropanols **4** and **7** relative to the alkylamidotropanols **8** and **9** (and also for the difference in reactivity between **4** and **7**). The arylamides are more reactive because electron donation from the aromatic π–system increases the nucleophilicity of the electronegative atoms of the amide group.



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The above reaction provides an extremely facile one pot synthesis of phenylphosphonate monoester analogues of the transition state in the hydrolysis of cocaine. An otherwise difficult reaction is facilitated by an intramolecular transfer of a phosphoryl group and, whereas intramolecular participation of amide groups in the hydrolysis of certain phosphonate esters is well documented,[9] an example of intramolecular assistance by an amide to phosphonate ester synthesis is unusual.

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