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BIOMIMETIC FORMATION OF TROPIC ACID ESTERS

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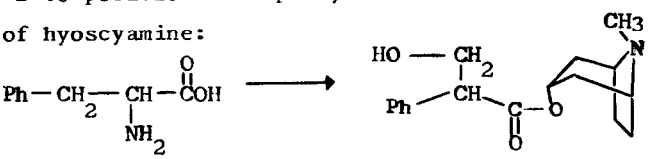
The biochemical origin of the tropic acid moiety of atropine and related alkaloids has attracted interest as a result of the definitive studies of Leete and Louden on the incorporation of ^{14}C labeled phenylalanine into hyoscyamine in Datura stramonium plants (1). These studies have shown that the conversion of phenylalanine to tropic acid apparently involves a carbonyl group shift from position 2 to position 3 of phenylalanine or a derivitive during the biosynthesis of hyoscyamine:

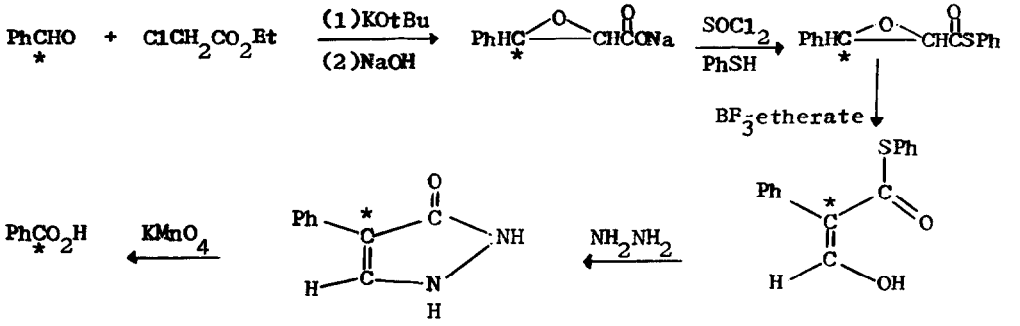


Attempts have been made to provide a laboratory model for this transformation. S.Yamada (2) and coworkers have discovered the nitrous acid induced conversion of phenylalanine to tropic acid. Leete (3) has substantiated the partial mechanism proposed by these workers showing, however, that this transformation does not apparently involve carbonyl group migration during the rearrangement and therefore it is not an acceptable laboratory model for tropic acid biosynthesis.

The critical step in a biochemically patterned synthesis of tropic acid esters is the rearrangement reaction involving carbonyl group migration. We have therefore attempted to design a substrate, structurally related to phenylalanine, that will allow for the conversion of the phenylalanine skeleton to the tropic acid carbon skeleton under mild conditions. We have found that the Lewis Acid catalyzed rearrangement of glycidic thiol esters (4) involves carbonyl group migration. For example phenyl trans-3-phenylthiolglycidate may be converted to the enol tautomer of phenyl 2-formylphenylthiolacetate. Examination of the chemical equation for this reaction does not establish whether or not the 3-phenyl group or the thiol ester group is the migrating

group during the rearrangement. We have undertaken appropriate tracer studies to clarify this point (Figure 1).

Figure 1



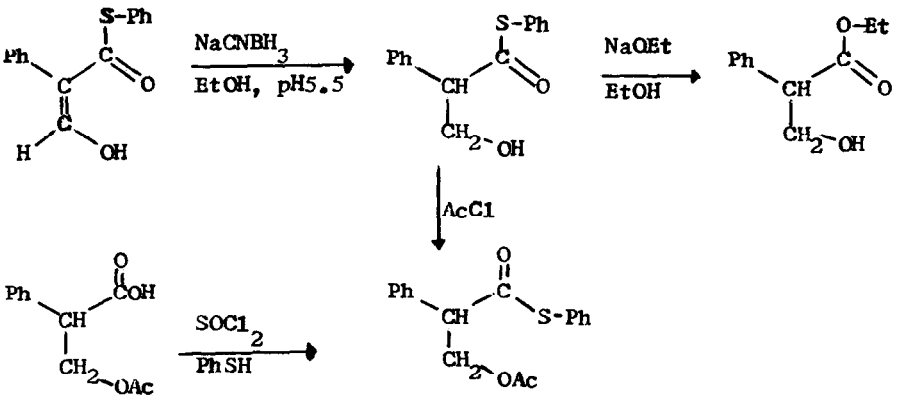
Compounds were identified by comparison with authentic samples. Phenyl trans-3-phenylthiolglycidate-3-^{14}C,4-phenylpyrazolone-4-^{14}C and benzoic acid-7-^{14}C have been recrystallized to constant activity. All the activity in the purchased benzaldehyde-7-^{14}C was shown to be located at position 7 by oxidation to benzoic acid which was decarboxylated to form CO_2(isolated as $BaCO_3$ for counting).

Benzaldehyde-7-^{14}C was converted to phenyl trans-3-phenylthiolglycidate-3-^{14}C (5.4×10^5dpm/mm) using literature methods (5,4). Rearrangement in the presence of BF_3-etherate in ether solvent provided phenyl 2-formylphenylthiolacetate which was converted to 4-phenylpyrazolone-4-^{14}C (5.2×10^5dpm/mm) with hydrazine hydrate in ethanol. Essentially all the ^{14}C activity was located at the 4 position of the 4-phenylpyrazolone as demonstrated by $KMnO_4$ oxidation to benzoic acid-7-^{14}C (5.0×10^5dpm/mm). These results support the conclusion that the thiol ester group migrates from position 2 to position 3 during the rearrangement of phenyl trans-3-phenylthiolglycidate to phenyl 2-formylphenylthiolacetate.

We have found that sodium cyanoborohydride allows for the selective reduction of the β-aldehyde group without destroying the thiol ester group in β-carbonyl thiol ester derivatives. Unlabeled rearrangement product, phenyl 2-formylphenylthiolacetate, was converted to the thiol ester of tropic acid (Figure 2) by reduction with excess sodium cyanoborohydride in ethanol (adjusted to pH 5.5 with acetic acid) over a 3 hr. period in 67% yield. Phenyl thioltropate (NMR(CCl_4-TMS) - 7.22 δ(s,10H,C_6H_5-), 3.50-4.10 δ(m,4H,-$\dot{C}HCH_2OH$); IR(neat) - 3390cm^{-1},1692cm^{-1}; Analysis $C_{15}H_{14}O_2S$; Calc. C:69.74, H:5.46,

S:12.41; Found C:69.60, H:5.34, S:12.26) was converted with acetyl chloride to phenyl 3-acetoxy-2-phenylthiolpropionate (m.p.59-61 (recrys. $CHCl_3$-benzene); NMR(CCl_4-TMS) - 7.18 δ (s,10H,C_6H_5-), 3.80-4.52 δ (m,3H,-$\overset{|}{C}HCH_2O$-),1.85 δ (s,3H,CH_3-); IR(neat) - 1740cm^{-1},1700cm^{-1}; Analysis $C_{17}H_{16}O_3S$; Calc. C:67.98, H:5.37, S:10.68; Found C:68.29, H:5.31, S:10.50) whose structure was established by independent synthesis employing 3-acetoxy-2-phenylpropionic acid, (6) thionyl chloride and benzenethiol.

Figure 2



The phenyl thioltropate was converted to ethyl tropate with sodium ethoxide in ethanol.

In conclusion our results provide support for Spenser's suggestion (7) that cinnamic acid is involved in the biosynthesis of tropic acid esters. This pathway may involve an enzyme catalyzed rearrangement of 3-phenylglycidate coenzyme A thiol ester which may be formed <u>in vivo</u> by epoxidation of a cinnamate coenzyme A thiol ester. It is interesting that ethyl 3-phenylglycidate undergoes BF_3 catalyzed rearrangement with proton migration providing ethyl 3-phenylpyruvate although ethyl glycidic esters substituted with an additional carbon group at the 2 or 3 position undergo rearrangement with carbethoxy migration (8). It is also noteworthy that 2,3-epoxycarbonyl systems are found in nature (9) although the glycidic thiol ester group has not previously been isolated from a natural system to our knowledge.

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