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Pictet-Spengler Condensations in Refluxing Benzene

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Summary

A variety of 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines have been synthesized utilizing a Pictet-Spengler condensation in a non-aqueous system, without the addition of acid. This new method affords significantly increased yields of the 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines compared to aqueous acid/methanol systems, especially for acid labile aldehydes.

The earliest general route to the 1,2,3,4-tetrahydro-β-carboline system was first described by Tatsui (1,2) and Akabori and Saito (3) and was modeled on the Pictet-Spengler tetrahydro isoquinoline synthesis (4). The synthesis consists of a Mannich reaction between tryptamine or tryptophan derivatives with an aldehyde in dilute mineral acid. Further illustrations of the scope of this synthesis are mentioned in recent reviews by Abramovitch and Spenser (5) and by Stuart (6). More recently, Kametani has described a synthesis of this type under milder conditions without acid catalysis for acid sensitive isoquinolines (7) and benzopyrans (8).

We have had to carry out a number of Pictet-Spengler reactions with several aldehydes and α-keto acids in connection with studies in our laboratory directed toward the synthesis of several potential antihypertensive agents (9). The yields with acid labile aldehydes have been inconsistent and generally quite low (10,11). Repeated attempts in our laboratory generally gave yields below those reported in the literature (10,11). To circumvent this problem we have developed a method for conducting the same condensations in a nonaqueous system, without addition of acid. When tryptophan methyl ester derivatives were reacted with various aldehydes or α-keto acids in refluxing benzene or benzene/dioxane (see Table 1) very good yields of the 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines were isolated. In each case the reaction proceeded with little or no decomposition of starting material or product compared to the aqueous system. Moreover, these reactions have been scaled up with no significant loss in yield.

This represents a distinct improvement over previous methods for performing this condensation. The labile aldehyde, ethyl-3-formylpropionate, provided excellent yields of the product whereas the methanol/acid system gave poor yields of the tetrahydro derivative.

A typical procedure is demonstrated as follows for the reaction of N_a-methyl, N_b-benzyl tryptophan methyl ester with 2-oxo-glutaric acid.

To a refluxing solution of N_a-methyl, N_b-benzyl tryptophan methyl ester (6.70 g, 0.021 mole) in 100 ml of benzene, was added 2-oxo-glutaric acid (3.44 g, 0.023 mole) in 1,4 dioxane (50 ml). The mixture was refluxed for 20 hours, and the H_2O collected by means of a Dean-Stark trap. Removal of solvent gave an orange oil which crystalized from methanol/benzene to give 4.5 g of the monoacid I (R_1 = CH_3, R_2 = Bz). Silica gel chromatography of the mother liquor gave an additional 3.7 g. Total yield 8.2 g (.0202 mole).

All structures were verified by spectroscopy (NMR, IR. MS) and comparison with authentic samples prepared in the methanol/acid system as illustrated in the literature. This new method provides the pathway for reaction of aldehydes which contain acid labile functions (*e.g.*, esters, acetals) with little or no decomposition.

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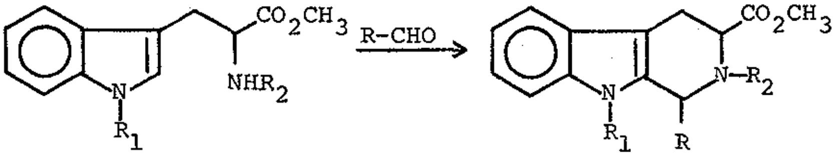
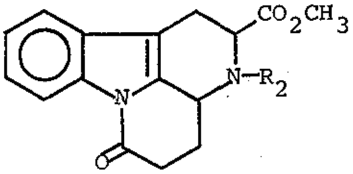
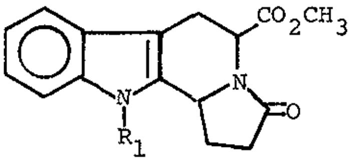
Table 1



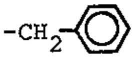
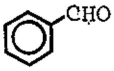
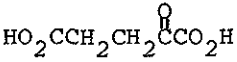
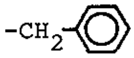
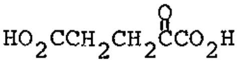
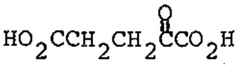
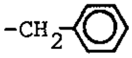
I



II



III

Aldehyde or α-Keto Acid	R_1	R_2	Solvent	Product	Yield	Yield ROH/H^+
	H	H	benzene	I[d]	85	73
	CH_3	H	benzene	I	75	--
$C_2H_5CO_2CH_2CH_2CHO$	CH_3		benzene	I	75	59[a,b]
	H	H	benzene	I[d]	95	90
 $HO_2CCH_2CH_2\overset{O}{\overset{\|}{C}}CO_2H$	CH_3		benzene/dioxane	I	97	--
 $HO_2CCH_2CH_2\overset{O}{\overset{\|}{C}}CO_2H$	H	H	benzene	III	80	40[c]
 $HO_2CCH_2CH_2\overset{O}{\overset{\|}{C}}CO_2H$	H		benzene/dioxane	I, II	23(I) 50(II)	--

[a] In our hands yields of this reaction were 50%. [b] See Ref 10. [c] See Ref 12. [d] Mixture of *cis* and *trans* isomers.

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12 The reaction was run in ethanol using the hydrochloride salt.

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