Synthesis of 1,2,3,4-Tetrahydro-β-carbolines

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Summary

The Pictet-Spengler condensation of acid labile aldehydes with N_b-benzyl tryptophan methyl ester and N_b-benzyl tryptamine has been carried out with carbonyl compounds such as glyoxal diethylacetal and ethyl-3-formylpropionate under non-protic conditions. The condensation in aprotic media does not occur with the free base, tryptamine, but works quite well for N_b-benzyl tryptamine. A study of the influence of various N_b-alkyl groups on the ease of cyclization has been explored. This has resulted in synthesis of β-carbolines, such as 1-salicyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (5b), which were previously very difficult to prepare.

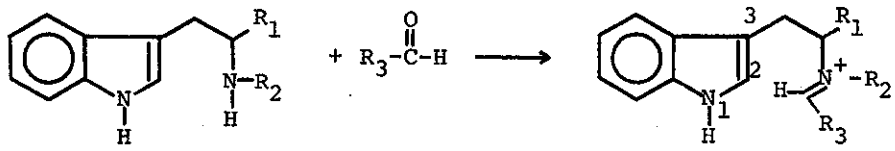
During studies directed toward the construction of potential antihypertensive agents we had occasion to perform several Pictet-Spengler (1) reactions with acid-labile aldehydes. When tryptophan methyl ester hydrochloride (1a) was heated with either ethyl-3-formylpropionate (2) or glyoxal diethylacetal (3) in aqueous methanol, poor yields of the 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines 2 and 3 were isolated, respectively. In the glyoxal case intractable tars were also obtained. However, when tryptophan methyl ester (1b) was stirred in refluxing benzene (4) with either

of the aforementioned aldehydes much better yields of the β-carbolines 2 and 3 were isolated. This is in direct contrast to the behavior of tryptamine (1c), which in the aprotic solvent, benzene, gave no tetrahydro-β-carboline, but which did yield the desired tricyclic species when heated with the same aldehydes in aqueous acidic media.

Two possible mechanisms have been proposed for the Pictet-Spengler condensation of tryptamine derivatives with aldehydes: one pathway (a) involves initial reaction at the three position of indole to yield a spiroindolenine intermediate (5) which then rearranges to the tetrahydro-β-carboline, while condensation by path (b) is postulated to occur by initial attack at position two of the indole leading to the β-carboline by loss of a proton at C-2 of the indole (6). Regardless of which mechanism may operate, the driving force in the cyclization can be viewed as the attack of the π electrons of the 2,3-indole double bond on the electrophilic imminium ion $\overset{H}{\underset{R}{\diagdown}}C{=}N^{+}\overset{R}{\underset{H}{\diagup}}$ in aqueous acid or the electrophilic imine $\overset{H}{\underset{R}{\diagdown}}C{=}N{-}R$ when the reaction is carried out with tryptophan methyl ester in aprotic solvents.

The failure of the Schiff base of tryptamine to cyclize in refluxing benzene versus the facile cyclization for the analogous reaction with tryptophan methyl ester can be rationalized by examination of the pK_a values for the two bases; tryptamine, pK_a = 10.2 (7), tryptophan methyl ester, pK_a = 7.29 (8). Clearly, the carbon-nitrogen double bond in the tryptamine case is less electrophilic for the nitrogen carries a higher electron density than that found for the tryptophan methyl ester "imine" intermediate.

SCHEME I



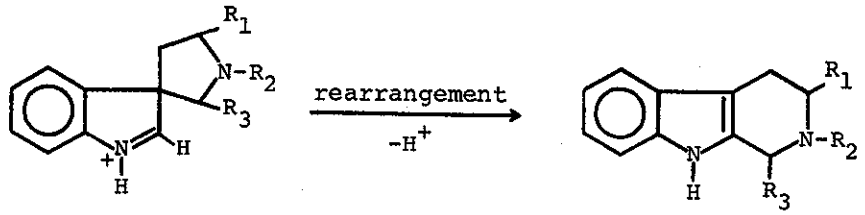
1a, $R_1 = CO_2CH_3$, $R_2 = H \cdot HCl$

1b, $R_1 = CO_2CH_3$, $R_2 = H$

1c, $R_1 = H$, $R_2 = H$

1d, $R_1 = H$, $R_2 = Bz$

1e, $R_1 = CO_2CH_3$, $R_2 = Bz$



2, $R_1 = CO_2CH_3$, $R_2 = H$, $R_3 = CH_2CH_2CO_2Et$

3, $R_1 = CO_2CH_3$, $R_2 = H$, $R_3 = HC(OEt)_2$

4, $R_1 = H$, $R_2 = Bz$, $R_3 = Ph$

5a, $R_1 = CO_2CH_3$, $R_2 = Bz$, $R_3 =$

5b, $R_1 = CO_2CH_3$, $R_2 = H$, $R_3 =$

To test this hypothesis, N_b-benzyl tryptamine (1d) was prepared. Schiff base formation with aldehydes now would lead to an enamine $\rightleftarrows$ imminium ion equilibrium mixture; the latter tautomer would bear a full positive charge on nitrogen.

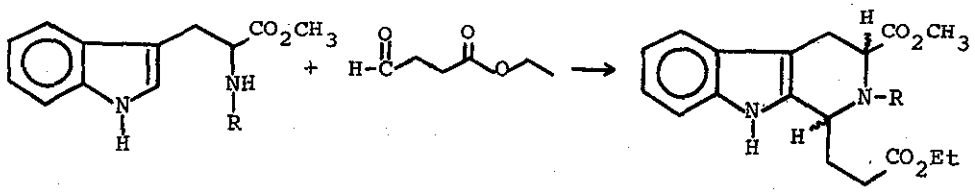
Indeed, heating 1d with benzaldehyde in refluxing benzene, provided a quantitative yield of the 1-phenyl-1,2,3,4-tetrahydro-β-carboline (4); no Pictet-Spengler product was formed when tryptamine, itself, was heated with benzaldehyde in the aprotic medium. The inductive effect of alkyl groups on the course of this reaction further supports our findings. Examination of the yields in Table I illustrates that the N_b-benzyl tryptophan methyl ester (1e) provides higher yields of the β-carbolines than the standard (R = H). Furthermore, the N_b-isopropyl derivative leads to lower yields of product. This is in accord with the electron releasing properties of the isopropyl group in contrast to electron withdrawal by the benzyl moiety (9). In fact, the N_b-benzyl derivatives have consistently provided a higher yield of β-carboline than their monosubstituted counterparts (Table I, R = H) and they reacted with aldehydes at a faster rate.

This method provides a facile route to 1-substituted-1,2,3,4-tetrahydro-β-carbolines from labile aldehydes; one more experiment deserves special mention. The carbonyl group of the aldehyde, salicylaldehyde, is not as electrophilic as that of benzaldehyde, because of the mesomeric effect of the hydroxyl group. For instance, tryptophan methyl ester condenses readily, as mentioned before, with benzaldehyde in aprotic media but does not give the tetrahydro-β-carboline (5b) with salicylaldehyde. Moreover,

salicylaldehyde polymerizes in acidic solution; consequently the β-carboline derivative (5b) of this carbonyl compound has not been obtained previously in greater than 3% yield (10). However, when N_b-benzyl tryptophan methyl ester was heated with salicylaldehyde in refluxing benzene a 62.5% yield (11) of 5a was isolated; catalytic debenzylation then provided 1-salicyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (5b) in 58% overall yield.

It has been difficult in the past in protic media to correlate the electron density on the aliphatic nitrogen with the ease of cyclization, for protonation of nitrogen could always occur from solvent; however, performing the reaction in refluxing benzene or dioxane eliminates this complication. The reactions of ethyl-3-formylpropionate, glyoxal diethylacetal and salicylaldehyde with either N_b-benzyl tryptophan methyl ester or N_b-benzyl tryptamine demonstrate the potential of this condensation in aprotic media (12).

TABLE I



R	Yield
isopropyl	42%
H	65%
benzyl	80%

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References

1 G. Tatsui, J. Pharm. Soc. Japan, 1928, 48, 453; G. Tatsui, J. Pharm. Soc. Japan, 1929, 49, 749; K. Stuart, Heterocycles, 1975, 3, 223; W. M. Whaley and T. R. Govindachari, Org. Reactions, 1951, 6, 151.

2 N. Yoneda, Chem. Pharm. Bull., 1965, 13, 1231.

3 K. Grohman and P. Noire, 172nd National Meeting of the American Chemical Society, San Francisco, August 30-September 3, 1976, Abstract 236.

4 J. Sandrin, D. Soerens, L. Hutchins, E. Richfield, F. Ungemach, and J. M. Cook, Heterocycles, 1976, 4, 1101.

5 A. H. Jackson and P. Smith, Chem. Commun., 1967, 264.

6 J. B. Hester, J. Org. Chem., 1964, 29, 2864; R. A. Abramovitch and I. D. Spenser, "Advances in Heterocyclic Chemistry," A. R. Katritzky, Ed., Academic Press, New York, 1964, p. 79.

7 D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth, London, 1965, p. 239.

8 R. W. Hay and L. J. Porter, J. Chem. Soc. (B), 1967, 1261.

9 R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley and Sons, New York, 1956, p. 591.

10 F. Hamaguchi, T. Nagasaka, and S. Ohki, Yakagaku Zasshi, 1974, 94, 351.

11 No attempt to maximize the yield of this reaction has been made. In a parallel study it was found that the aldehyde, p-methoxybenzaldehyde, did not react with tryptophan methyl ester in refluxing benzene but did provide a 15% yield when the reaction was carried out in refluxing p-xylene. The N_b-benzyl derivative

provided a 40% yield of the β-carboline when heated in refluxing p-xylene with the same aldehyde. p-Nitro benzaldehyde reacted rapidly with tryptophan methyl ester in protic or aprotic media.[12] In this procedure, the water from the condensation is removed azeotropically by means of a Dean-Stark trap. Aldehydes of low molecular weight (i.e., acetaldehyde) do not work well for the carbonyl compound distills into the D-S trap. A benzene/dioxane solvent mixture can be employed for benzene insoluble substrates.

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