

β-AMINOSTYRYL DERIVATIVES VIA FOLATE MODELS. APPROACH TO
YOHIMBANE SKELETON

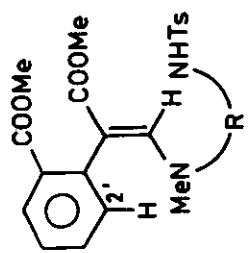
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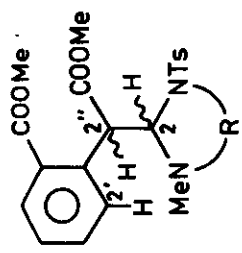
Abstract - 2-Methoxycarbonyl-(α-methoxycarbonyl-β-tryptaminyl)-styrene, prepared by transfer of $\text{CH}_2\text{OOC}-2-\text{C}_6\text{H}_4\text{CH}(\text{COOCH}_3)\text{CH}$ via a methylenetetrahydrofolate model, to tryptamine, yields the pentacyclic system of yohimbane in two steps.

We have recently reported on the utility of methylenetetrahydrofolate models in several synthetic objectives^{3a-c}. It was demonstrated that models derived from substituted benzaldehydes provided a facile synthesis of yohimbane derivatives^{3b}. Since benzaldehydes, with desired substituents, are not always accessible with facility, attention was directed to other aryl derivatives which would lead to "equivalent" methylenetetrahydrofolate models. One such model was visualized in the general type of adducts derived from anions of 1a,b and salts 2a,b. Exploratory experiments showed that the anion of 1a does not add to salts 2a or 2b; presumably because of suppressed nucleophilicity due to delocalization of the charge in the benzoate ester moiety. The possibility was considered that an electron withdrawing group on the side-chain methyl moiety (of 1a) might enhance the nucleophilicity of the desired anion.

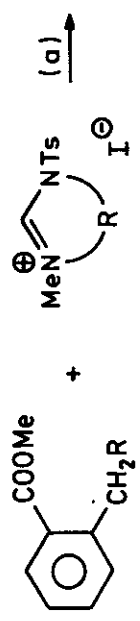
In this communication we present the synthesis of models 3a,b (from diester 1b) and their application in the facile construction of the yohimbane skeleton. The models 3a,b were prepared as crystalline or amorphous substances by adding salts 2a,b⁴ to the anion of 1b in THF (-30°C, 30 min). It should be recognized that both 3a and 3b represent two diastereomers, in each case. The structure of one of the diastereomers of 3a (2R, 2''R), mp 138-139°C, was established by X-Ray crystallography⁵. In case of 3b, only one diastereomer was observed, the structure of which has not yet been established⁶. During the isolation of 3a,b, varying amounts of the corresponding enamine esters 4a [mp 132-134°C; PMR (CD₃CN) 2.23 s 3H (NCH₃), 2.38 s 3H (Ar-CH₃), 7.12-7.5 m 5H (=CH + 4 arom. protons)] and



4



3



2

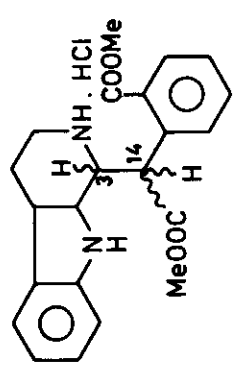
1a R = H

1b R = COOMe

a R = -CMe₂CH₂-

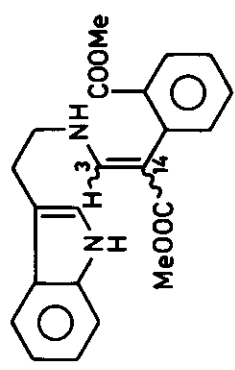
b -(CH₂)₃-

(b)



6 a,b

(c)



5

(a) LDA, THF, -30° ; (b) tryptamine / AcOH, MeCN, Δ ; (c) HCl-Et₂O / MeOH / R.T.

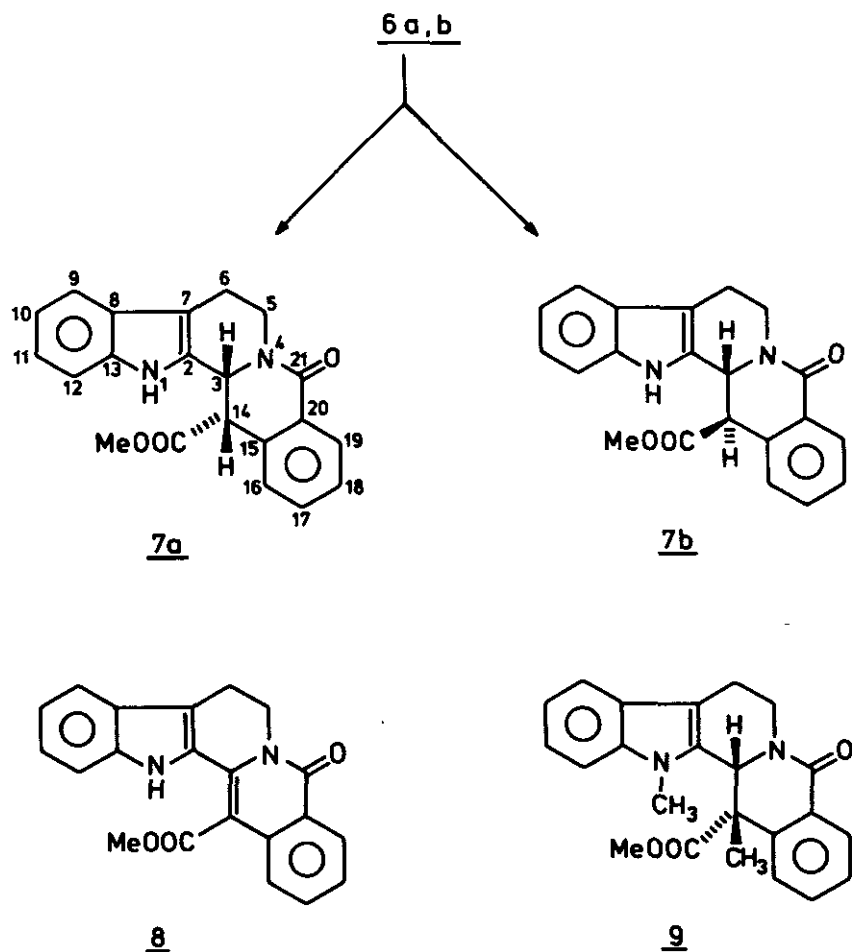
4b [amorphous; PMR (CD_3CN) 2.29 s 3H (NH_3), 2.35 s 3H (Ar-CH_3), 7.39 s 1H ($=\text{CH}$)] were obtained. The E-configuration of β -aminoacrylic esters 4a and 4b was established by Nuclear Overhauser experiments. Thus irradiation of the N-methyl groups in 4a,b resulted in signal enhancement of the C_2 -protons.

When pure 3a, 3b or mixtures of 3a+4a, 3b+4b were allowed to react with tryptamine (MeCN, AcOH, Δ) the carbon atom C(2) of the models was transferred -with its ligands- to the amino group of tryptamine to yield a mixture of isomeric β -amino esters 5⁷ (90%, E:Z = 1:2, PMR (C_6D_6) significant chemical shifts, E 2.37 t J = 6.5 2H [$\text{C}_6-(\text{H}_2)$], 2.70 dt J = 6.5, 6.4 2H [$\text{C}_5-(\text{H}_2)$], 4.09-4.17 m 1H (NH), 7.7 d J = 13.5 1H ($\text{C}_3\text{-H}$); Z 2.57 t J = 6.5 2H [$\text{C}_6-(\text{H}_2)$], 2.89 dt J = 6.5, 6.4 2H [$\text{C}_5-(\text{H}_2)$], 6.35 d J = 13.1 1H ($\text{C}_3\text{-H}$), 8.45-8.55 m 1H (NH)).

In contrast to the sequence of cyclizations (AB \rightarrow ABD \rightarrow ABCD), employed by us earlier for the synthesis of indoloquinolizidine derivatives^{3a}, for construction of the yohimbane skeleton, the sequence AB \rightarrow ABC \rightarrow ABCDE, starting from 5, proved to be the preferred strategy. Treatment of 5 (isomeric mixture) with acid ($\text{HCl-Et}_2\text{O/MeOH}$, R.T., 5 min) resulted in its cyclization to two diastereomeric β -carboline derivatives 6a (major diastereomer) and 6b (minor diastereomer) in the ratio 4:1. The individual diastereomers were not isolated but could be recognized in the mixture by their characteristic PMR spectra ($\text{CDCl}_3 + 1 \text{ eq. NaOD}$) 6a: 4.73 d J = 7.6 1H ($\text{C}_3\text{-H}$), 5.45 D J = 7.6 1H ($\text{C}_{14}\text{-H}$); 6b: 4.79 d J = 9.6 1H ($\text{C}_3\text{-H}$), 5.23 d J = 9.6 1H ($\text{C}_{14}\text{-H}$). The data did not, however, allow stereochemical assignments to the individual diastereomers.

The construction of ring D (6a,b \rightarrow 7a,b) was accomplished by a $\text{Et}_3\text{N/AcOH}$ catalyzed cyclization of 6a,b in benzene (R.T. overnight). The two isomers 7a and 7b were formed in an overall yield of 90% (7a/7b = 4). The predominant isomer 7a was isolated as a crystalline product, mp 237°C (dec.), MS: Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3 = 346$, Found: M^+ 346). The cis stereochemistry of 7a has been assigned on the basis of PMR and Nuclear Overhauser differential spectra. 7a PMR (DMSO-d_6): 3.19 s 3H (COOCH_3), 4.66 d J = 4.1 1H ($\text{C}_{14}\text{-H}$), 5.44 d J = 4.1 1H ($\text{C}_3\text{-H}$, the signal shows line-broadening due to homoallylic coupling with one of the C_6 -protons), 7.47 d J = 8.1 1H ($\text{C}_{16}\text{-H}$), 11.14 s 1H indole N-H. When $\text{C}_3\text{-H}$ is irradiated $\text{C}_{14}\text{-H}$ exhibits a positive signal, while irradiation of $\text{C}_{14}\text{-H}$ results in positive signals for $\text{C}_3\text{-H}$, indole N-H and $\text{C}_{16}\text{-H}$. The trans isomer, mp 222°C (dec.) 7b shows the following characteristic peaks in the PMR (DMSO-d_6) spectrum: 3.77 s 3H (COOCH_3), 4.75-4.85 m 2H ($\text{C}_{14}\text{-H} + \text{one of } \text{C}_5\text{-H}$), 10.88 s 1H (indole N-H). If the

cyclization is carried out at higher temperature ($\sim 50^{\circ}\text{C}$) the reaction mixture yields variable amounts of the oxidation product 8, mp $233\text{--}235^{\circ}\text{C}$. Structure of compound 8 followed from its spectral data: IR (CHCl_3): 3430 (NH), 1714 (C-C-COOMe), 1648 (-N-C=O); PMR (DMSO-d_6): 3.10 m 2H [$\text{C}_5\text{-(H}_2\text{)}$], 3.98 s 3H (COOCH_3), 4.39 m 2H [$\text{C}_5\text{-(H}_2\text{)}$], 8.34 d $J = 7.9$ 1H ($\text{C}_{19}\text{-H}$), 10.46 s 1H (N-H). To examine the possibility of substitution at the α -position of the ester function of 7a,b, the cis isomer 7a was allowed to react with methyl iodide, using NaH as base. The product of this reaction was found to be a single substance 9⁸ (80%), indicating that the anion alkylated stereospecifically. The above-mentioned sequence of transformations represents a facile method of construction of the yohimbane system and its stereospecific substitution at C_{14} .



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REFERENCES

* To whom all enquiries should be addressed.

1. Models of Folate Coenzymes XII. Part XI. *Tetrahedron Letters*, in press.
2. Taken in part from the doctorate dissertation of A.R. Stoit; University of Amsterdam.
3. (a) A.R. Stoit and U.K. Pandit, *Heterocycles*, 20, 2129 (1983); (b) H.C. Hiemstra, H. Bieräugel, M. Wijnberg and U.K. Pandit, *Tetrahedron*, 39, 3981 (1983); (c) H. Bieräugel, R. Plemp and U.K. Pandit, *ibid.*, 39, 3987 (1983).
4. For 2a see H. Bieräugel, R. Plemp, H.C. Hiemstra and U.K. Pandit, *Tetrahedron*, 39, 3971 (1983). 2b was made in an analogous manner.
5. Details of the structure of diastereomer 3a and the X-Ray data will be presented elsewhere.
6. The structure of diastereomer 3b, without stereochemical assignment is based upon its PMR spectrum. Salients chemical shifts (CD_3CN): 5.87 d J = 11.3 1H (C_2-H), 5.38 d J = 11.3 1H ($C_{2''}-H$), 2.26 s 3H (NCH_3), 6.80 d J = 7.6 1H ($C_{2'}-H$).
7. Since 5 and its further transformation products contain all the carbon atoms of the yohimbane skeleton, the alkaloid numbering is used for these compounds.
8. 9: mp 251-253°C PMR ($DMSO-d_6$): 2.10 s 3H (NCH_3), 3.38 s 3H ($COOCH_3$), 3.69 s 3H ($C_{14}-CH_3$), 5.45 broad s 1H (C_3-H) are significant. Irradiation of $C_{14}-CH_3$ results in a positive NOE for C_3-H and $C_{16}-H$. It should be mentioned that the signal for $C_{14}-CH_3$ appears at low field due to deshielding by the aromatic ring and the ester carbonyl, whose conformational mobility is restricted.

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