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B-AMINOSTYRYL DERIVATIVES VIA FOLATE MODELS. APPROACH TO YOHIMBANE SI(ELEN
Axel R. Stoit2 and Upendra K. Pandit*
Organic Chemistry Laboratory, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Abstract - 2-Methoxycarbonyl-(a-methoxycarbonyl-β-tryptaminyl)-
styrene, prepared by transfer of \( \text{CH}_2\text{OOC-2-C}_6\text{H}_4\text{CH(COOCH}_3\text{)} \) 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 objectives3a–c. It was demonstrated that models derived from
substituted benzaldehydes provided a facile synthesis of yohimbane derivatives3b.
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 \( 1\text{a,b} \) and salts \( 2\text{a,b} \). Exploratory experiments showed that the anion of \( 1\text{a} \) does not add to salts \( 2\text{a} \) or \( 2\text{b} \);
presumably because of suppressed nucleophilicity due to delocalization of the
charge in the benzoate ester moiety. The possibility was considered that an elec-
tron withdrawing group on the side-chain methyl moiety (of \( 1\text{a} \)) might enhance the
nucleophilicity of the desired anion.

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

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4b [amorphous; PMR (CD$_3$CN) 2.29 s 3H (NH$_3$), 2.35 s 3H (Ar-CH$_3$), 7.39 s 1H (=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 2a, 2b or mixtures of 2a+2b, 2b+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 5 (90%, E:Z = 1:2, PMR (C$_6$D$_6$)) significant chemical shifts, E 2.37 t J = 6.5 2H [C$_6$-(H$_2$)], 2.70 dt J = 6.5, 6.4 2H [C$_5$-(H$_2$)], 4.09-4.17 m 1H (NH), 7.7 d J = 13.5 1H (C$_7$-H); Z 2.57 t J = 6.5 2H [C$_6$-(H$_2$)], 2.89 dt J = 6.5, 6.4 2H (C$_5$-(H$_2$)], 6.35 d J = 13.1 1H (C$_7$-H), 8.45-8.55 m 1H (NH)). In contrast to the sequence of cyclizations (AB → ABD → ABCD), employed by us earlier for the synthesis of indoloquinolizidine derivatives 3a, for construction of the yohimbane skeleton, the sequence AB → ABC → ABCDE, starting from 2, proved to be the preferred strategy. Treatment of 2 (isomeric mixture) with acid (HCl·Et$_2$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 (CDCl$_3$ + 1 eq. NaOD) 6a: 4.73 d J = 7.6 1H (C$_2$-H), 5.45 d J = 7.6 1H (C$_4$-H); 6b: 4.79 d J = 9.6 1H (C$_2$-H), 5.23 d J = 9.6 1H (C$_4$-H). The data did not, however, allow stereochemical assignments to the individual diastereomers.

The construction of ring D (6a,b → 7a,b) was accomplished by a Et$_3$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 C$_{21}$H$_{18}$N$_2$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 (C$_{14}$-H), 5.44 d J = 4.1 1H (C$_2$-H, the signal shows line-broadening due to homoallylic coupling with one of the C$_6$-protons), 7.47 d J = 8.1 1H (C$_{16}$-H), 11.14 s 1H indole N-H. When C$_2$-H is irradiated C$_{14}$-H exhibits a positive signal, while irradiation of C$_{14}$-H results in positive signals for C$_2$-H, indole N-H and C$_{16}$-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 (C$_{14}$-H + one of C$_5$-H), 10.88 s 1H (indole N-H). If the

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cyclization is carried out at higher temperature (~50°C) the reaction mixture yields variable amounts of the oxidation product 8, mp 233-235°C. Structure of compound 8 followed from its spectral data: IR (CHCl₃): 3430 (NH), 1714 (C=O-COOMe), 1648 (-N-C=O); PIR (DMSO-d₆): 3.10 m 2H [C₆(H₂)], 3.98 s 3H (COOCH₃), 4.39 m 2H [C₅(H₂)], 8.34 d J = 7.9 1H (C₁₉-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 NaN₃ as base. The product of this reaction was found to be a single substance 9 (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 C₁₄.
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REFERENCES

* To whom all enquiries should be addressed.

2. Taken in part from the doctorate dissertation of A.R. Stoit; University of Amsterdam.
5. Details of the structure of diastereomer 3a and the X-Ray data will be presented elsewhere.
6. The structure of diastereomer 2b, without stereochemical assignment is based upon its FMR spectrum. Salients chemical shifts (CD ClON): 5.87 d $J = 11.3$ 1H (C2-H), 5.38 d $J = 11.3$ 1H (C2'-H), 2.26 s 3H (NCH3), 6.80 d $J = 7.6$ 1H (C2'-H).
7. Since 2 and its further transformation products contain all the carbon atoms of the yohimbane skeleton, the alkaloid numbering is used for these compounds.
8. 2: mp 251-253°C FMR (DMSO-d6): 2.10 s 3H (NCH3), 3.38 s 3H (COOH3), 3.69 s 3H (C14-CH3), 5.45 broad s 1H (C2-H) are significant. Irradiation of C14-CH3 results in a positive NOE for C2'-H and C16'-H. It should be mentioned that the signal for C14-CH3 appears at low field due to deshielding by the aromatic ring and the ester carbonyl, whose conformational mobility is restricted.

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