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ISOLATION OF THE ROTATIONAL ISOMERS OF AN AMIDE

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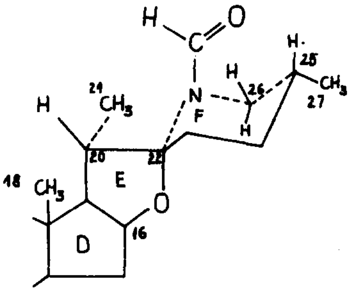
Restricted rotation about the N - C partial double bond in amides has been the subject of several investigations. At present the main factors determining the simultaneous occurrence of the two rotational amide isomers as well as their rates of interconversion are well established (1).

It is to be expected that under "favourable" stereochemical conditions the rotational barrier may be as high as to practically prevent at room temperature the interconversion between the cis and trans isomers. Recently Mannschreck reported (2) the isolation of an amide isomer by rapid cooling of the equilibrium mixture, and other attempts are being made to isolate both conformers in pure form (3). It is the purpose of this letter to report the isolation of two amide isomers which, in our opinion, are best assigned as the cis and trans rotational conformers.

The amide, O,N-diformate of 5α-solasodanol /I/ being the subject of other studies carried out in our laboratory, has been prepared in abs. chloroform solution of 5α-solasodanol at +15° by slow addition of formic - acetic mixed anhydride. Thin-layer chromatography revealed the presence in approximately equal amounts of two reaction products (isomers **A** and **B**) which could then be separated by fractional crystallization and column chromatography. Both of them proved by chemical analysis and IR spectra to be O,N-diformates, and are characterized by the following physical constants:

isomer **A**: m.p. 222 - 224° ; $[\alpha]_D^{20} = -21,2°$ (in $CHCl_3$)

isomer **B**: m.p. 202 - 204° ; $[\alpha]_D^{20} = -69,6°$ (in $CHCl_3$) .



I

In principle, there may be two kinds of isomerism for **A** and **B** which can equally result in a difference in the optical rotatory power: (a) configurational isomerism at C-22 owing to the opening of ring F during the formylation; and (b) rotational cis - trans isomerism about the N-C partial double bond producing a new asymmetry centre at the nitrogen atom. The extremely mild reaction conditions chosen by us, however, make the first alternative highly improbable.

A distinction between the two cases was possible examining the proton resonance spectra of the two isomers *). The chemical shifts of the main assignable protons as compared with those of the parent molecule are presented in TABLE I.

The change of the configuration at C-22 should involve an equatorial to axial transition of the C-27 methyl group. In this case one has to expect a downfield shift of about 0,1 ppm for the C-27 methyl doublet (4,5), accompanied by a simultaneous decrease of the vicinal coupling constant of the axial C-26 methylene proton. The data presented in TABLE I show that neither of these expectations are met. The most important differences in the proton resonance spectra giving an idea about the nature of the isomerism in question are to be found in the chemical shifts of the C-26 axial and equatorial, C-20 and N-CO-H protons. It seems to us reasonable to ascribe these

TABLE I

	C-19	C-18	C-21	C-27	C-16	C-20	C-26_{ax}	C-26_{equ}	NCO-H
5α-solasodanol	0,82	0,79	0,94	0,85	4,21	<2,0	2,59	2,59	-
Isomer A	0,83	0,86	1,13	0,91	4,32	2,4	3,13 (J_{aa} = 7,5)	3,95 (J_{ea}=3,5)	8,68
Isomer B	0,83	0,84	1,15	0,88	4,30	~2,0	2,2 (J_{aa}=7,0)	4,22 (J_{ea}=3,0)	8,50

Chemical Shifts (δ) measured in $CDCl_3$

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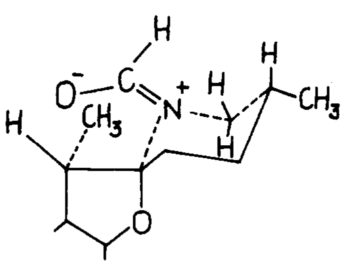
*) Proton resonance spectra were recorded at 60 Mc/s with an AEI RS2 spectrometer using 10% w/v $CDCl_3$ and C_6D_6 solutions.

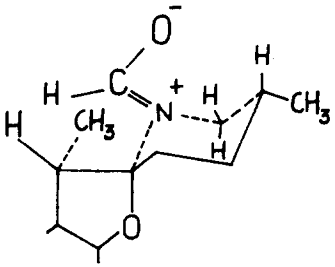
changes to the different rotational positions of the amide carbonyl group. Considering the magnitude of the chemical shifts of these particular protons in the two isomers, the situation may be represented by the approximate partial structures II and III. This assignation is also supported by the measured chloroform - benzene solvent shifts.



II

Isomer *A*

trans



III

Isomer *B*

cis

Examination of the molecular models reveals that the formation of the amides must be accompanied by a considerable distortion of the side-chain geometry. It can also be seen that interconversion of the two isomers by means of rotation around the N - C bond is practically impossible. We made an attempt to determine the rotational activation energy by recording the proton resonance spectra of a 1 : 1 mixture of the two isomers at higher temperature. Up to 100° we could observe no change arising from an increased rate of interconversion. Unfortunately above 100° the *cis* isomer and above 130° the *trans* compound suffered decomposition thus preventing measurements at elevated temperatures.

It should be mentioned that in the case of tomatidine, the related isomeric pair of the parent amine, only one diformate is obtainable (m.p.: 215 - 217° ; $[\alpha]_D^{20} = -4,3^{\circ}$, in $CHCl_3$) under the same reaction conditions. Similarly, one single amide was found with both 5α-solasodanol and tomatidine when the amide proton was substituted with bulkier alkyl groups such as CH_3 or C_2H_5 . Interpretation of these observations from the point of view of the side-chain stereochemistry of the parent alkaloids will be discussed elsewhere (5).

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