SATURATED NITROGEN HETEROCYCLES.

# 13.* MECHANISM OF FORMATION OF HYDROXYALKYLPYRROLIDINES BY CATALYTIC HYDROGENATION OF FURAN AMINES

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The formation of hydroxyalkylpyrrolidines from furan amines has been modeled using deuterium exchange. The stages of the reaction were established by comparing the $^{13}C$ NMR spectra of the nondeuterated and deuterated pyrrolidinylalkanols, and the similarly formed tetrahydrofuran amines.

Discussions of the mode of formation of hydroxyalkylpyrrolidines from furan amines by catalytic hydrogenation of the latter in acid media have appeared previously [2, 3].

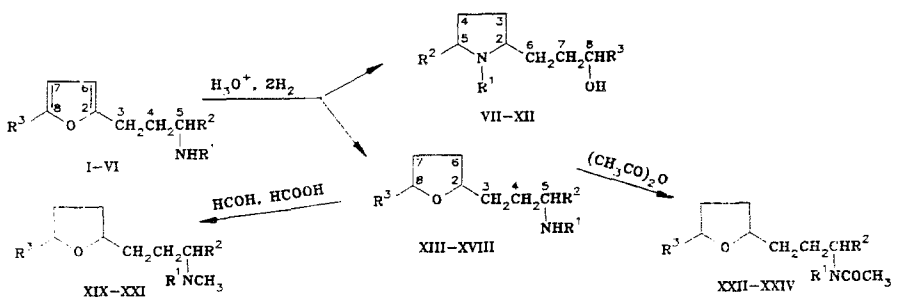
Examination of the $^{13}C$ NMR spectra of a large series of hydroxyalkylpyrrolidines [1], the tetrahydrofuran amines formed as by-products, and the deuterated products isolated from the reaction mixture when the reaction was modeled in heavy water and deuteroacids, enabled the mode of formation of pyrrolidinylalkanols from furan amines to be clarified. The previous use of IR spectroscopy for this purpose was found to be erroneous, since the proposed course of the reaction was based on the ratios of the amounts of deuterium present in the product molecules, without taking into account the location of the deuterium in the hydroxyalkylpyrrolidine [3, 4].

It is also noteworthy that $^{13}C$ NMR spectroscopy has undoubted advantages over proton resonance spectroscopy in these studies, the latter giving a spectrum in the region of the chemical shifts of the methylene protons which is complex and difficult to interpret.

The subjects chosen for this study were the furan amines (I) and (V). The choice of these types of amines was made on the basis that their conversion into pyrrolidinylalkanols is carried out in media of differing polarity, giving ambiguous results [5, 6].

The $^{13}C$ NMR spectra of the pyrrolidinylalkanols have been reported [1]. In order to identify the by-products, the tetrahydrofuran amines (XIII-XXI) were obtained, together with their acetyl derivatives (XXII-XXIV) (Scheme 1).

Scheme 1




I, VII, XIII $R^1=R^3=H$, $R^2=CH_3$; II, VIII, XIV, XXII $R^1=R^2=CH_3$, $R^3=H$; III, IX, XV, $R^1=R^3=H$; $R^2=i\text{-}C_4H_9$; IV, X, XVI $R^1=R^3=H$, $R^2=t\text{-}C_4H_9$; V, XI, XVII $R^1=C_6H_5$, $R^2=R^3=H$; VI, XII, XVIII, XXIV $R^1=R^2=R^3=CH_3$; XIX, XXIII $R^1=CH_3$, $R^2=i\text{-}C_4H_9$, $R^3=H$; XX $R^1=CH_3$, $R^2=t\text{-}C_4H_9$, $R^3=H$; XXI $R^1=R^3=CH_3$, $R^2=H$

*For Communication 12, see [1].

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TABLE 1. Chemical Shifts (δ, ppm) of the Carbon Atoms of Tetrahydrofuran Derivatives

| Compound | $C_{(2)}$ | $C_{(3)}$ | $C_{(4)}$ | $C_{(5)}$ | $C_{(6)}$ | $C_{(7)}$ | $C_{(8)}$ | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| XIII | 79,36, 79,23 | 32,56, 32,47 | 36,83, 36,69 | 46,77 | 31,49, 31,43 | 25,78 | 67,44 | — | 23,91 | — | — |
| XIV | 79,19, 79,00 | 32,65, 32,34 | 30,10, 29,80 | 58,86, 58,59 | 31,18, 31,11 | 25,41 | 67,14 | 40,09 | 13,16, 12,94 | — | — |
| XV | 79,50, 79,29 | 32,31, 32,47 | 36,31, 36,13 | 48,94 | 31,51, 31,42 | 25,75, 25,72 | 67,51 | — | 47,79, 47,73 ($CH_2$); 24,56, 23,56 (CH); 22,10 ($CH_3$) | — | — |
| XVI | 79,63, 79,23 | 33,91 | 32,85, 32,75 | 58,99 | 31,42, 31,30 | 25,63 | 67,44 | — | 42,17 (CH); 26,09 ($CH_3$) | — | — |
| XVII | 79,01 | 33,01 | 44,81 | — | 31,26 | 25,57 | 67,49 | 158,69, 112,59 (o), 129,00(*m*), 116,90 (p) | — | — | — |
| XVIII | 79,66, 79,45 | 33,56, 33,44 | 30,33, 30,04 | 59,21, 58,95 | 31,48, 31,42 | 32,99 | 75,03 | 40,43 | 21,49 | 13,41, 13,28 | — |
| XIX | 79,46, 79,26 | 33,13, 32,87 | 26,27, 25,90 | 61,34, 61,13 | 31,19, 31,13 | 25,42 | 67,24 | 39,88 | 38,47 ($CH_2$); 24,92 (CH); 22,67, 22,49 ($CH_3$) | — | 39,88 |
| XX | 79,84, 79,62 | 35,94 | 23,37, 23,22 | 72,60 | 31,52 | 25,74 | 67,52 | 43,56, 43,51 | 37,43, 37,38 (CH); 27,93 ($CH_3$) | — | — |
| XXI | 78,72 | 33,80 | 23,99 | 59,44 | 31,21 | 32,73 | 74,47 | 44,93 | — | 21,20 | 44,93 |
| XXII | 78,81, 78,52 | 32,08, 32,00 | 27,76 | 60,81 | 31,38 | 25,71 | 67,55 | 38,48 | 13,05 | — | 175,68 (CO); 22,37 ($CH_3$) |
| XXIII | 79,29, 79,10 | 33,30, 33,06 | 26,65, 26,43 | 61,85, 61,56 | 31,62 | 25,87 | 67,47 | 39,67 | 38,81 ($CH_2$); 25,34 (CH); 23,14, 22,65 ($CH_3$) | — | 174,99 (CO); 22,31 ($CH_3$) |
| XXIV | 78,85, 78,60 | 32,68, 32,52 | 27,64 | 61,04 | 31,28 | 32,84 | 75,44 | 38,52 | 21,38 | 13,14, 13,03 | 175,47 (C=O); 22,02 ($CH_3$) |

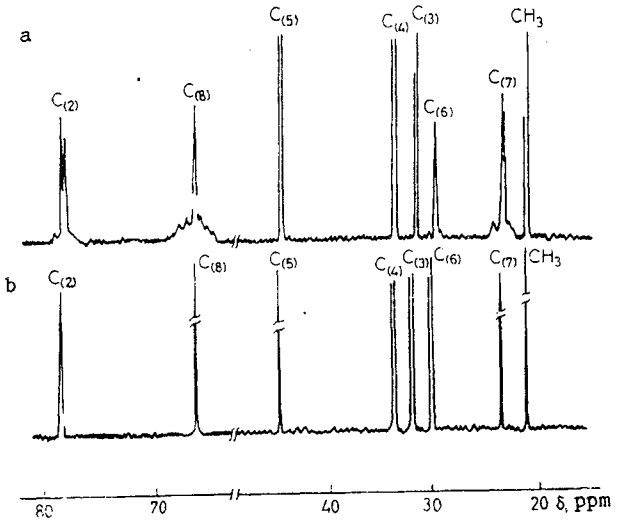



Fig. 1

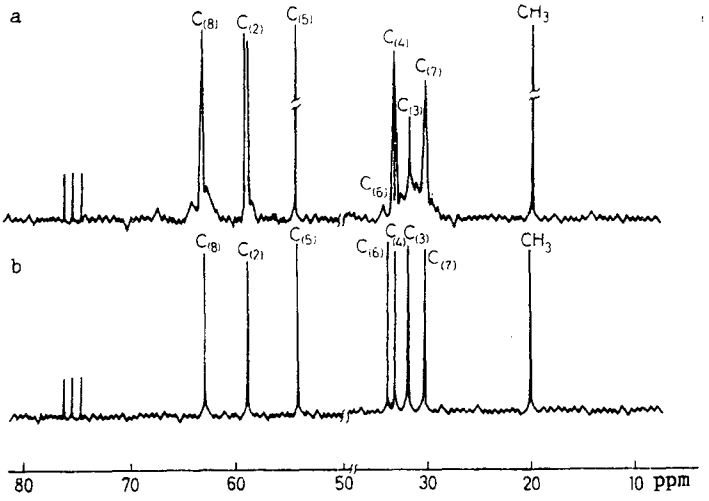



Fig. 2

Fig. 1. $^{13}C$ NMR Spectrum of 3-amino-1-tetrahydrofurfuryl-butane (XIII). a) Deuterated, b) undeuterated.

Fig. 2. $^{13}C$ NMR Spectrum of 3-(5-methyl-2-pyrrolidinyl)-propanol (VII). a) Deuterated, b) undeuterated.

The interpretation of the $^{13}C$ NMR spectra of the tetrahydrofuran amines and their derivatives was based on the off-resonance data, calculation of the general features of the low-field shifts of the carbon atoms located at the electronegative atoms, the α-, β-, and γ-effects of the substituents, and literature information [7].

Tetrahydrofuran amines, like the hydroxyalkylpyrrolidines, show characteristic chemical shifts for the carbon atoms* $C_{(2)}$ 78.52-79.85, $C_{(6)}$ 31.10-31.60, and $C_{(3)}$ 32.00-33.90 ppm, and when the α-position of the heterocycle is free, $C_{(8)}$ 67.14-67.52 and $C_{(7)}$ 25.42-25.87 ppm.

Introduction of a methyl substituent into the α-position of the tetrahydrofuran ring shifts the signals for atoms $C_{(8)}$ and $C_{(7)}$ to lower field in accordance with the α- and β-effects of the substituents.

The presence of two asymmetric centers results in the appearance of spatial isomers with similar properties in similar proportions, as shown by the splitting of some of the signals for (XIII-XVI), (XVIII-XX), and (XXII-XXIV) (Table 1).

*The carbon atoms of the tetrahydrofuran amines are designated in the same way as the corresponding carbon atoms of the pyrrolidinylalkanols.

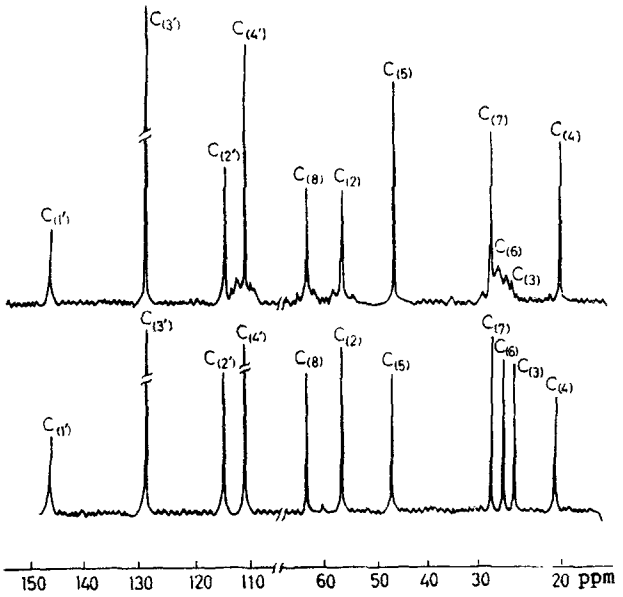



Fig. 3. $^{13}C$ NMR Spectrum of 3-(1-phenyl-2-pyrrolidinyl)-propanol (XI). a) Deuterated, b) undeuterated.

The hydroxyalkylpyrrolidines and tetrahydrofuran amines, obtained from the furylalkylamines, showed a similar mode of deuterium exchange when the reaction was modeled in heavy water and deuteroacids, irrespective of the type of metallic contact (skeletal nickel promoted by ruthenium, or borided nickel promoted by ruthenium).

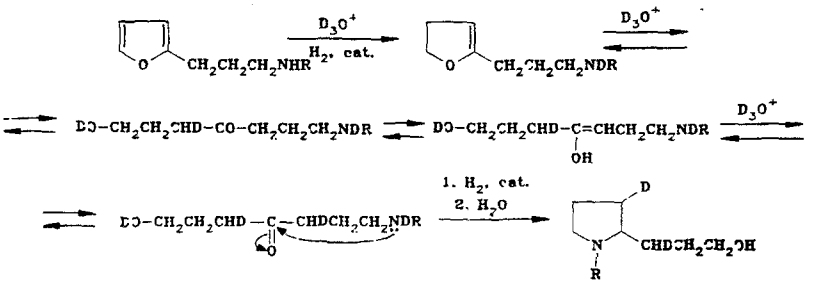
For example, the pyrrolidinylalkanol and tetrahydrofuran amine obtained from the amine (I) contained deuterium in positions corresponding to the furan ring, indicating partial electrophilic isotope exchange in the original heterocycle (Figs. 1 and 2). This is confirmed by the decrease in the intensity of the signals, and the appearance alongside of multiplets. As would be expected, the greatest amount of deuteration occurred at the α-position of the furan ring [at $C_{(8)}$]. The ratios of the intensities of the signals for the respective deuterated and nondeuterated carbons in the pyrrolidinylalkanol (VII) and the tetrahydrofuran amine (XIII) coincided, except for positions 6 and 3, averaging 3:1 and 1:3 for $C_{(8)}$ and $C_{(7)}$, respectively. Unlike (XIII), deuterium exchange in the hydroxyalkylpyrrolidine (VII) took place to some extent in position 3, and almost completely in position 6.

In the pyrrolidinylalkanol (XI), obtained from the weakly basic aromatic furylalkylamine (V), the azocyclization of which occurs in media of low polarity, deuterium exchange occurred in positions 3 and 6 only. This shows that the conditions for electrophilic isotope exchange in the original compound do not correspond (Fig. 3).

The absence of deuterium in positions $C_{(4)}$ and $C_{(5)}$ of the reaction products (VII), (XI), (XIII), and (XVII) shows that unactivated methylene protons are resistant to deuterium exchange.

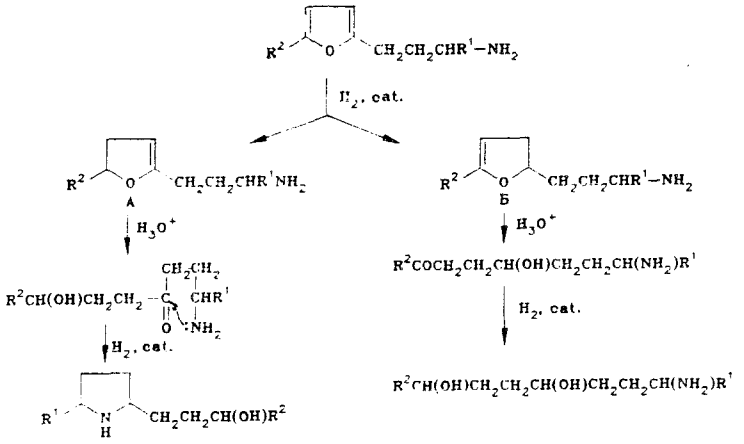
The sequence of reactions as established by the experimental data is shown in Scheme 2.

Scheme 2



This mechanism affords a good explanation for the formation of aminodiols as by-products with α-methylated furan amines. When substituents are present at both the double bonds of the furan ring [3, 8], hydrogenation is hindered, and occurs competitively at either of the double bonds. Hydrolytic cleavage of the resulting dihydrofurans A and B affords aminoalcohols, of which one can give the pyrrolidinylalkanol only, and the other the aminodiol (Scheme 3).

Scheme 3



Hence, heterocyclization of furan amines precedes hydrogenation taking place at the catalyst surface, which is probably responsible for the predominant formation of the cis-isomers of the hydroxyalkylpyrrolidines [2]. Bulky substituents in the side chain, by hindering the hydrogenation of the second double bond in the heterocycle, facilitate its hydrolytic cleavage, and consequently increased yields of the pyrrolidinylalkanols, which explains the experimental results obtained previously [5].

## EXPERIMENTAL

$^{13}C$ NMR Spectra were obtained on a Varian FT-80A (20 MHz) in $CDCl_3$ in impulse accumulation mode followed by Fourier transformation. The starting furan amines (I-VI), the tetrahydrofuran amines (XIII-XV) and (XVIII), and the acetyl derivatives (XXII-XXIV) were obtained as described in [5, 6, 8-11]. The previously unknown amines (XVI) and (XVII) were obtained by the method reported in [5].

1-(2-Tetrahydrofuryl)-4,4-dimethyl-3-aminopentane (XVI, $C_{11}H_{23}NO$). bp 90-91°C (13.3 hPa); $n_D^{20}$ 1.4554. IR spectrum: 3340 ($\nu_{NH}$), 1650 $cm^{-1}$ ($\delta_{NH}$).

N-Phenyl-3-(2-tetrahydrofuryl)-1-aminopropane (XVII, $C_{13}H_{19}NO$). bp 142-144°C (5.3 hPa); $n_D^{20}$ 1.5532. IR spectrum: 3410 ($\nu_{NH}$), 1630 ($\delta_{NH}$), 750, 690 $cm^{-1}$ ($\delta_{=CH}$).

N,N-Dimethyl-1-(2-tetrahydrofuryl)-5-methyl-3-aminohexane (XIX, $C_{13}H_{27}NO$). Obtained by alkylating (XV) with an excess of formic acid and formalin by the method described in [6]. bp 128-130°C (13.3 hPa), $n_D^{20}$ 1.4500. IR spectrum: 1380, 1370 $cm^{-1}$ ($\delta_{C(CH_3)_2}$) (doublet, intensity ratio 1:1).

N,N-Dimethyl-1-(2-tetrahydrofuryl)-4,4-dimethyl-3-aminopentane (XX, $C_{13}H_{17}NO$). Obtained similarly. bp 110-111°C (21 hPa); $n_D^{20}$ 1.4522. IR spectrum: 1390, 1365 $cm^{-1}$ ($\delta_{C(CH_3)_3}$) (doublet, intensity ratio 1:2).

N,N-Dimethyl-(5-methyl-2-tetrahydrofuryl)-3-aminopropane (XXI, $C_{10}H_{21}NO$). bp 70-72°C (5.3 hPa), $n_D^{20}$ 1.4560.

Hydrogenation of 1-(2-Furyl)-3-aminobutane (I) in the Presence of $D_2O$ and DCl. A mixture of 10 g (0.07 mole) of the amine (I), 20 ml of heavy water, and 1 g of skeletal nickel promoted with ruthenium was acidified with cooling with 35% DCl (7.6 ml) to pH 4, and hydrogenated in a rotary steel autoclave of capacity 150 ml at an initial hydrogen pressure of 50 atm and a temperature of 70-80°C until the calculated amount (33 atm) of hydrogen had

been taken up (14 h). The hydrogenate was worked up as described in [10]. Repeated fractionation in vacuo gave the deuterated products (XIII) in a yield of 1.3 g (13%), bp 110-111°C (6.6 hPa), $n_D^{20}$ 1.4680.

Hydrogenation of N-Phenyl-3-(2-furyl)-1-aminopropane (V) in the Presence of $D_2O$ and DCl

A solution of 10 g (0.05 mole) of the amine (V), 10 ml of heavy water, and 15 ml of dry dioxane was acidified with cooling with DCl (2.3 ml) to pH 4, and hydrogenated in a 150 ml rotating steel autoclave in the presence of 1 g of skeletal nickel promoted with ruthenium, at an initial hydrogen pressure of 50 atm and a temperature of 70°C for 15 h. The hydrogenate was worked up as described in [6]. Repeated fractionation in vacuo gave 1.0 g (10%) of deuterated product (XVII), bp 174-175°C (6.6 hPa), $n_D^{20}$ 1.5690. Similar results were obtained when borided nickel promoted by ruthenium was used [12].

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