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Catalytic Synthesis of 7-Azaoctahydropyrrocolines

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Further study of the field of application of the reaction described earlier by us—catalytic intramolecular dehydration of furan and tetrahydrofuran amines, leading to the formation of 1,2-dihydrodipyrroles and pyrrolizidines (^{1})—has made it possible to establish that it has a more general character and can be extended to tetrahydrofuran diamines.

As a result of dehydration of the latter, perhydro derivatives are formed of

pyrrolo-$[1, 2\text{-}a]$-pyrazine-(7-azapyrrocoline) (I) —compounds (^{2,4}), only recently obtained in the free state, although some of its derivatives have long been known (^{2}). Systems consisting of condensed pyrrolidine and piperazine rings with a nitrogen atom common to both nuclei have been studied hardly at all. Meanwhile, they occur in molecules of certain natural alkaloids (^{3}) and are of interest as a basis for the synthesis of potentially biologically active substances.

The furan diamines required for further synthesis, as we have shown, can readily be obtained by reductive amination of furfural and its homologs with ethylenediamine. On hydrogenation they give, in good yields, the corresponding tetrahydrofuran diamines. Catalytic dehydration of furan diamines has so far not given positive results. However, dehydration of tetrahydrofuran diamines proceeds normally and leads to the formation of 7-azaoctahydropyrrocolines, or, according to another nomenclature, 1,4-diazabicyclo-$[4, 3, 0]$-nonanes.

The syntheses were carried out according to the following scheme:

$$\text{R-furyl-CHO} + \text{H}_2\text{N}{-}\text{CH}_2{-}\text{CH}_2{-}\text{NH}_2 \xrightarrow[\text{Ni},\,80^\circ]{\text{H}_2}$$

$$\longrightarrow \text{R-furyl-CH}_2{-}\text{NH}{-}\text{CH}_2{-}\text{CH}_2{-}\text{NH}_2 \qquad \begin{array}{l} \text{II } R = \text{H}, \\ \text{III } R = \text{CH}_3 \end{array}$$

$$\xrightarrow[\text{Ni},\,150^\circ]{\text{H}_2} \text{R-tetrahydrofuryl-CH}_2{-}\text{NH}{-}\text{CH}_2{-}\text{CH}_2{-}\text{NH}_2 \qquad \begin{array}{l} \text{IV } R = \text{H}, \\ \text{V } R = \text{CH}_3 \end{array}$$

$$\xrightarrow[\text{Al}_2\text{O}_3,\,\text{ZrO}_2]{-\text{H}_2\text{O}} \text{7-azaoctahydropyrrocoline derivative} \qquad \begin{array}{l} \text{VI } R = \text{H}, \\ \text{VII } R = \text{CH}_3 \end{array}$$

With the exception of II, all the compounds described in the present paper have been synthesized for the first time. Some previously unknown derivatives of

7-azaoctahydropyrrocolines, as well as of furan and tetrahydrofuran diamines, were also obtained. Investigations in this field are continuing.

Experimental Part*

N-Furfurylethylenediamine (II). A solution of 87 g of the hydrated form of ethylenediamine in 200 ml of methanol was charged into a rotating autoclave, and then, with stirring, 34 g of furfural and 8 g of Raney nickel were added there. Temperature 80°, initial hydrogen pressure 100 atm. The calculated amount of hydrogen is absorbed. The catalyst was filtered off, after which the methyl alcohol and excess ethylenediamine were distilled off on a water bath under reduced pressure. Ether was added to the residue; a brownish precipitate separated. After drying over caustic potassium hydroxide, the ethereal solution was filtered free of alkali and precipitate, the ether was distilled off, and the residue was distilled in vacuum. Yield 33.8 g (68.2%). Colorless viscous liquid with a faint amine odor.

Similarly, **N-(α'-methylfurfuryl)ethylenediamine (III)** was synthesized from α'-methylfurfural and ethylenediamine.

N-Tetrahydrofurfurylethylenediamine (IV). A solution of 25 g of II in 63 ml of absolute alcohol and 5 g of Raney nickel was introduced into a rotating autoclave. Initial hydrogen pressure 100 atm, temperature 150°. After distillation of the alcohol and fractional distillation of the residue in vacuum, 21.7 g (84.4%) of (IV) was obtained. **N-(α'-methyltetrahydrofurfuryl)ethylenediamine (V)** was synthesized analogously by hydrogenation of (III). The most important physical properties and analyses of the furan and tetrahydrofuran diamines obtained by us are given in Table 1.

Table 1

No. of compound	Compound	b.p. (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calc.	Empirical formula	C, % found	C, % calc.	H, % found	H, % calc.	N, % found	N, % calc.	Yield, %
II	N-Furfurylethylenediamine	103–103.5° (10)	1.5029	1.0470	39.57	40.06	$C_7H_{12}N_2O$	59.60	59.97	8.66	8.63	19.61	19.99	68.2
III	N-(α'-Methylfurfuryl)ethylenediamine	111.5 (10)	1.4997	1.0194	44.47	44.68	$C_8H_{14}N_2O$	59.54	62.30	8.66	9.15	19.08	18.17	73.0
IV	N-Tetrahydrofurfurylethylenediamine	106–107 (10)	1.4750	0.9888	41.03	40.99	$C_7H_{16}N_2O$	62.45	58.30	9.40	11.18	8.00	19.43	84.4

No. of compound	Compound	b.p. (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calc.	Empirical formula	C, % found	C, % calc.	H, % found	H, % calc.	N, % found	N, % calc.	Yield, %
V	N-(α′-Methyltetrahydrofurfuryl)ethylenediamine	105–106 (10)	1.4662	0.9524	46.03	45.61	$C_8H_{18}N_2O$	62.32	60.72	9.24	11.47	18.40	17.70	79.2
VI	7-Azaoctahydropyrrocoline	68–70 (10)	1.4940	0.9679	37.96	37.67	$C_7H_{14}N_2$	66.26	66.62	11.20	11.18	22.48	22.20	30.3
VII	3-Methyl-7-azaoctahydropyrrocoline	70–73 (10)	1.4875	0.9452	42.70	42.29	$C_8H_{16}N_2$	66.30	68.52	11.25	11.50	22.24	19.98	32.7

* With the participation of V. M. Levin and T. P. Semenova.

Dehydration of the diamines was carried out in a flow apparatus of the usual type at 300–315°. The catalyst was aluminum oxide activated with zirconium dioxide and preliminarily calcined for 3 hr at 700°. For the experiments, 35 cm^3 of catalyst with a grain diameter of about 3 mm was used. Nitrogen was passed through the reactor at a rate of 800–1000 ml/hr.

7-Azaoctahydropyrrocoline (VI). 18.7 g of (IV) was passed through the reactor over 2 hr 30 min. The catalyzate was a homogeneous yellowish-green liquid. After ether and solid KOH were added to the catalyzate, an aqueous layer separated after some time. The aqueous layer was discarded, and the ethereal layer was dried with caustic potash. The ethereal solution was then filtered, the ether was distilled off, and the residue was distilled in vacuum. Yield 4.97 g (30.3%).

Analogously, 3-methyl-7-azaoctahydropyrrocoline (VII) was synthesized from (V).

VI and VII are colorless mobile liquids with a strong odor resembling that of pyrrolizidines. They are soluble in water, alcohol, and ether. The most important physical properties and analyses of VI and VII are given in Table 1.

N,N′-Diacetyl derivatives of diamines (II–IV) were obtained as follows: the starting diamine, with cooling, was treated with a one-and-a-half-fold excess of acetic anhydride, after which the mixture was heated for 10 min at 100°. The excess acetic anhydride and acetic acid were distilled off on a water bath under reduced pressure. The residue was distilled in vacuum. All the diacetyl derivatives obtained (VIII–X) are nearly colorless, very viscous liquids, soluble in water.

N-Acetyl derivatives of 7-azaoctahydropyrrocolines were obtained by treating VI and VII with a one-and-a-half-fold excess of acetic anhydride, as described above. After heating, an aqueous KOH solution was added to the mixture until the reaction was strongly alkaline, and the reaction products were extracted with benzene. The benzene was distilled off and the residue was distilled in vacuum. The N-acetyl derivatives XI and XII are colorless liquids, soluble in water. The most important physical properties and analyses of the diacetyl and acetyl derivatives obtained are given in Table 2.

Table 2

N,N′-Diacetyl derivatives of furan and tetrahydrofuran diamines and N-acetyl derivatives of 7-azaoctahydropyrrocolines

No. of compound	Starting substance	B.p. (pressure in mm)	n_D^{20}	Empirical formula	C, % found	C, % calculated	H, % found	H, % calculated	N, % found	N, % calculated	Yield, %
VIII	II	165–168° (1)	1.5160	$C_{11}H_{16}N_2O_3$	59.30; 59.18	58.91	7.23; 7.33	7.19	12.33; 12.74	12.49	73.2
IX	III	180–182 (1)	1.5128	$C_{12}H_{18}N_2O_3$	60.18; 60.32	60.48	7.58; 7.57	7.61	11.32; 11.38	11.76	67.5
X	IV	192 (1)	1.4990	$C_{11}H_{20}N_2O_3$	58.10; 58.22	57.87	9.02; 9.16	8.83	11.81; 12.10	12.27	71.1
XI	VI	129–130 (5.5)	1.5060	$C_9H_{16}N_2O$	64.02; 64.51	64.24	9.51; 9.43	9.58	16.38; 16.20	16.65	50.0
XII	VII	98–100 (1)	1.4998	$C_{10}H_{18}N_2O$	66.38; 66.09	65.89	10.24; 10.02	9.95	14.90; 15.27	15.37	56.5

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Note: Figure translations are in progress. See original paper for figures.