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STUDIES OF 1-AZABICYCLO COMPOUNDS
IV. Catalytic Synthesis of 1-Azabicyclo [4.3.0] Nonane and 1-Azabicyclo [5.3.0] Decane Compounds*

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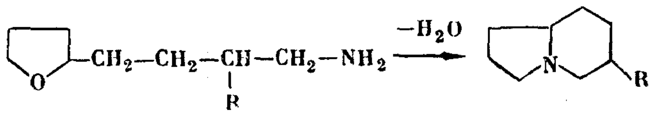
Furan and tetrahydrofuran amines with the amino group at position 4 or 5 in the side chain are intramolecularly dehydrated to the corresponding 1-azabicyclo compounds when passed over Al_2O_3-ZrO_2 catalyst at 325-330°.

Previous papers described intramolecular dehydration of furan and tetrahydrofuran amines having the amino group at position 3 [2, 3], as well as of some tetrahydrofuran diamines [4].

The work described in the present paper was undertaken to investigate the scope of the above reaction, and how its course is influenced by the position of the amino group on the side chain. It is shown below that dehydration of amines with the amino group at position 4 or 5 in the side chain is a practical route to 1-azabicyclo [4.3.0] nonane and especially 1-azabicyclo [5.3.0] decane compounds.

The previously described [2] general method of intramolecular dehydration over mixed Al_2O_3-ZrO_2 catalyst [4] was applied to 1-(α-tetrahydrofuryl)-4-aminobutane (I) and 1-(α-tetrahydrofuryl)-3-methyl-4-aminobutane (II). The temperature was measured at the middle surface part of the reactor tube.

Dehydration of the amines I and II gave octahydropyrrocoline (III) and 6-methyloctahydropyrrocoline in 54% and 34% yield respectively.

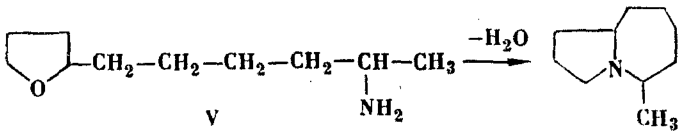


R = H I
R = CH_3 II

R = H III
R = CH_3 IV

The octahydropyrrocoline was identified by its elementary analysis, by determining its molecular refraction, and by comparing the properties of the base itself and of its picrate with those given in the literature [5-8].

Intramolecular catalytic dehydration of 1-(α-tetrahydrofuryl)-5-aminohexane (V) and 1-(α-furyl)-5-aminohexane (VI) proceeds with great difficulty. Apparently this can be put down to steric conditions for closure of the seven membered ring being unfavorable. Conversion of the amine V led to formation of 2-methyl-1-azabicyclo [5.3.0] decane (VII) in 15.4% yield.



V VII

However, this interesting reaction was accompanied by a number of side reactions. Passage of 14.4 g amine V over the catalyst gave 7.9 g catalyzate, 4.0 g of which consisted of nitrogen-free compounds, whose structures were not investigated. The catalyst in the front part of the tube showed heavy coking (after the run, the catalyst had gained 6.1 g).

IV and VII have two asymmetric carbon atoms, so that each can exist in two diastereoisomeric pairs of forms (any racemic pair is subsequently regarded as a single isomer). Unfixed thin-layer chromatography of IV and VII on alumina, using the solvent system ethyl acetate–hexane (1 : 6), led to separation of the isomers in the chromatogram (visualizer iodine vapor). Chromatography of the picrates of compounds IV and VII under exactly the same conditions showed that they consisted of mixtures of picrates of both isomers. When the picrates were chromatographed they de-

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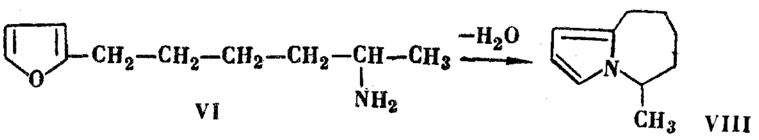
*For Part III see [1].

composed into the bases and picric acid. The latter, under the conditions referred to, remained at the beginning (see Fig.). Preparative separation of the isomers will be dealt with in a separate paper.

Proceeding by analogy with known cases [2, 9], it can be assumed that dehydration of 1-(α-furyl)5-aminohexane (VI) takes place according to the following equation



The dehydration product has been assigned the structure of 5-methyl-6, 7, 8, 9-tetrahydro-5H-pyrrolo [1, 2-a] azepine (VIII) from the method of synthesis, refraction data, positive Ehrlich reaction of a pyrrole unsubstituted in the α position, and IR and UV spectra data.

The IR spectrum contains absorption bands at 1562 and 1505 cm^{-1}, which correspond to pyrrole ring C=C valence vibrations [10], while the UV spectrum has an absorption maximum at 268 mμ (in 96% alcohol) (ε 264) which is characteristic for such pyrrole systems [9].

The furan and tetrahydrofuran amines with an amino group at position 4 or 5 required for the catalytic conversions were prepared by methods described in the literature [11-13].

In the syntheses of tetrahydrofuryl alkyl halides and nitriles of tetrahydrofuryl substituted carboxylic acids yields were improved; more accurate and more extensive data were obtained for their physical properties.

The Table gives the most important information for the compounds synthesized.

Properties of Compounds Prepared

Compound No.	Compound	Bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Formula	Found, %			Calculated, %			Yield, %
					Found	Calculated		C	H	N	C	H	N	
III	Octahydropyrrocoline*	67—68 (33)	0.8956	1.4718	39.13	38.68	$C_8H_{15}N$	76.75 76.33	11.99 11.96	10.72 10.63	76.74	12.09	11.19	54.4
IV	6-Methyloctahydropyrrocoline	73—74 (30)	0.8874	1.4698	43.76	43.30	$C_9H_{17}N$	77.66 77.71	12.16 12.25	9.65 9.70	77.63	12.31	10.06	33.6
VII	2-Methyl-1-azabicyclo [5, 3, 0] decane	74—77 (10)	0.9037	1.4777	47.98	47.92	$C_{10}H_{19}N$	78.29 78.27	12.49 12.61	8.98 9.04	78.36	12.50	9.14	15.4
VIII	5-Methyl-6, 7, 8, 9-tetrahydro-5H-pyrrolo[1, 2-a] azepine	92—93 (10.5)	0.9710	1.5220	46.87	46.99	$C_{10}H_{15}N$	81.26 81.25	10.28 10.25	8.56 8.59	80.48	10.13	9.38	21.4

*Literature data for III: bp 66—67°(18mm); n_D^{20} 1.4711 [5]; bp 71-72° (32mm); $n_D^{21.2}$ 1.4702 [6]; bp 86°(32mm); n_D^{21} 1.4697 [7]; bp 75°(63mm); $d_4^{10.5}$ 0.9074 [8].

Experimental

1-(α-Tetrahydrofuryl)-3-chloropropane (IX). Prepared by treating 1-(α-tetrahydrofuryl) propanol-3 [14] with thionyl chloride in a way similar to that described in the literature [15]. Yield of compound IX 60%, bp 53° (4 mm); d_4^{20} 1.0485; n_D^{20} 1.4588. Found: C 56.43, 56.14; H 8.59, 8.94; Cl 23.50, 23.67%; MR_D 38.74. Calculated for $C_7H_{13}ClO$: C 56.52; H 8.81; Cl 23.88%; MR_D 38.68.

1-(α-Tetrahydrofuryl)-3-chlorobutane (X). This was prepared similarly, from 1-(α-tetrahydrofuryl) butanol-3, yield 46%, bp 71° (6 mm); d_4^{20} 1.0126; n_D^{20} 1.4530. Found: C 58.96, 58.98; H 9.28, 9.37; Cl 21.63, 21.42%; MR_D 43.43. Calculated for $C_8H_{15}ClO$: C 59.03; H 9.28; Cl 21.82%; MR_D 43.46. The literature [15] gives: bp 58-60° (3 mm); d_4^{20} 0.9976; n_D^{20} 1.4505.

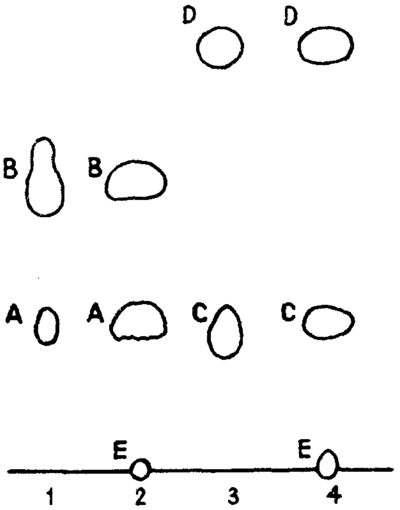
γ-(2-Tetrahydrofuryl) butyronitrile (XI). Prepared from compound IX and KCN, yield 17% calculated on the reacted IX, bp 116-117° (10 mm); n_D^{20} 1.4552. The literature [11] gives 115-116° (10 mm).

αMethyl-γ-(2-tetrahydrofuryl) butyronitrile (XII). Prepared similarly from compound X and KCN, yield 74.5% on the reacted X, bp 93-94° (3 mm); d_4^{20} 0.9569; n_D^{20} 1.4506. Found: N 8.84, 9.01%; MR_D 43.08. Calculated for $C_9H_{15}NO$: N 9.14%; MR_D 43.02.

The amine I was prepared by hydrogenating nitrile XI in the presence of Raney nickel, according to the method of [11], yield 75.2%. Bp 99-101° (12 mm); n_D^{20} 1.4615. The literature [11] gives bp 98° (12 mm).

Amine II was similarly prepared from the above nitrile XII; yield 80.4%, bp 86-88° (4 mm); d_4^{20} 0.9165; n_D^{20} 1.4575. Found: C 68.56, 68.22; H 12.47, 12.57; N 9.03, 8.90%; MR_D 46.78. Calculated for $C_9H_{19}NO$: C 68.74; H 12.18; N 8.91%; MR_D 46.63.

Octahydropyrrocoline (III). 11.72 g (0.08 mmole) amine I was passed through the reactor tube (surface temperature of latter 324-326°) in 1 hr 40 mm. In the receiver 8.96 g catalyzate (a greenish liquid) collected. On being worked up in the usual way [2] it gave 5.57 g (54.4%) compound III, a colorless mobile volatile liquid with an intense odor.



1) Compound VII (mixture of isomers); 2) picrate of compound VII; 3) compound IV (mixture of isomers); 4) picrate of compound IV (A, B - diastereoisomeric forms of VII; C, D - diastereoisomeric forms of IV; E - picric acid).

The picrate formed yellow flat needles (ex ethanol). Sparingly soluble in hot and cold alcohol. Mp 230-231° (decomp). Found: N 15.82, 15.74%. Calculated for $C_8H_{15}N \cdot C_6H_3N_3O_7$: N 15.81%. The literature gives: mp 233-234° [5]; 228-229° [6]; 231-232° (ex ethanol) [7]; mp 228.5° [8].

6-Methyloctahydropyrrocoline (IV). Compound IV (3.47 g) prepared from amine II by the usual method, was dissolved in 20 ml ether, and treated with 20 ml of a 13% aqueous solution of hydrochloric acid. The ether layer was rejected, the hydrochloric acid solution extracted with ether, after which solid KOH was added to the acid solution until it was strongly alkaline. The oil which came out was separated off, the solution extracted with ether, and extracts and oil bulked, then the ether solution was worked up in the usual way.

The picrate of the mixed isomers (C and D) formed yellow flaky crystals (ex alcohol). It was comparatively readily soluble in hot ethanol, mp 199-201°. Found: N 15.07, 15.42%. Calculated for $C_9H_{17}N \cdot C_6H_3N_3O_7$: N 15.21%.

2-Methyl-1-azabicyclo [5.3.0] decane (VII). Amine V was dehydrated at 325-329°. The material obtained by working up the catalyzate in the usual way, was purified as described above.

The mixture of picrates of isomers A and B formed crystals which were yellow small plates (ex ethanol) mp 193-195° (decomp). Found: N 14.92, 14.55%. Calculated for $C_{10}H_{19}N \cdot C_6H_3N_3O_7$: N 14.65%. The literature [16] gives mp 196° (ex methanol).

5-Methyl-6, 7, 8, 9-tetrahydro-5H-pyrrolo [1, 2-a] azepine (VIII). Prepared in the usual way from amine VI. Dehydration temperature 326-330°. Purification with 5% sulfuric acid left its constants practically unaltered.

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