SATURATED NITROGEN RING COMPOUNDS

II. Formation of Derivatives of Cyclopentanopyrrolidine, Octahydroindole, and Related Heterocyclic Systems, from Furfuryl-Substituted Cyclic Amines*

A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina

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Preparation of pyrrolidine derivatives by hydrogenating acid solutions of furan amines having the amino group at position 3, is extended to furfuryl-substituted cyclic amines. By this means are synthesized polycyclic systems hitherto undescribed in the literature, containing a pyrroldine ring with hydroxyalkyl and other substituents. Among these are derivatives of cyclopentanopyrrolidine, octahydroindole, etc.

Previously there was reported a new method of synthesizing α-pyrrolidylalkan-3-ols by hydrogenating acid solutions of furan amines with the amino group at the third carbon atom from the ring in the aliphatic side chain [1, 2, 3].

The present paper is concerned with a further investigation of the sphere of application of this reaction. With this in mind, a number of primary and secondary furfuryl-substituted cyclic amines with an appropriately located amino group were submitted to hydrogenation. The subjects of investigation were 1-(α-furfuryl)-2-aminocyclopentane, 1-(α-furfuryl)-2-aminotetralin, 1-(α-furfuryl)-2-aminoindane, and some primary and secondary furfurylcyclohexylamines. Experiments showed all these amines to be hydrogenated in acid solution by a mechanism previously postulated [1] for furan amines with the amino group in an aliphatic side chain. The reaction products are polycyclic alcohols of the cyclopentanopyrrolidine, octahydroindole, benzohexahydroindole, and indanopyrrolidine series.

Equations for the reaction are given following Table 1.

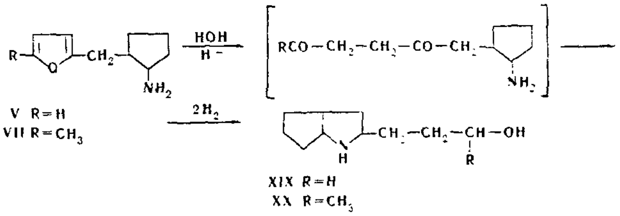
Since hydrolytic splitting of the furan ring is accompanied by straight hydrogenation of the double bonds of the same ring, amines containing the tetrahydrofuran ring and corresponding to the starting compounds, are also formed. Obviously, as in cases previously considered [1], the relative yields of the two products depend on the position and nature of the substituent at the α carbon atom of the side chain of the furan ring. The results of Table 1 show this.

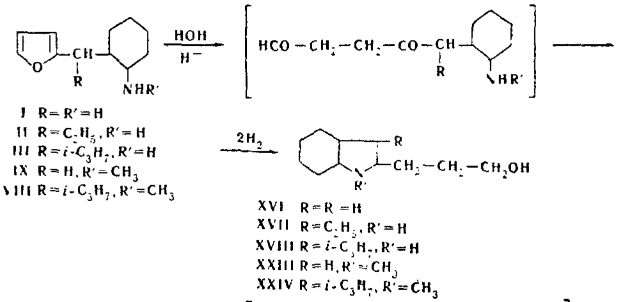
It is to be noted that from among the products of hydrogenation of 1-(5'-methyl-2'-furfuryl)-2-aminocyclopentane were isolated not only the corresponding tetrahydrofuran amine, and cyclopentanopyrrolidyl alcohol, but also 1-(1'-aminocyclopentyl-2')hexane-2,5-diol, probably arising by hydrogenation of the intermediate aminodicarbonyl compound arising in the process.

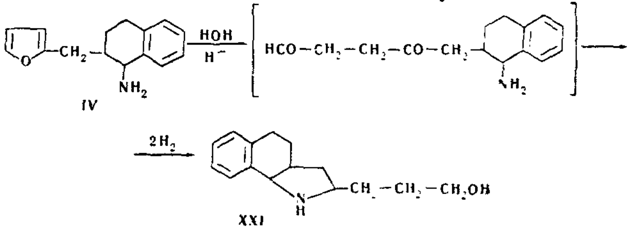
Table 1

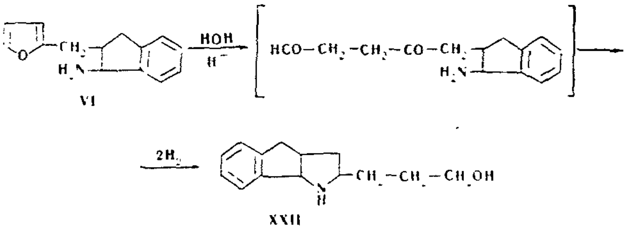
Yields of Various Products when Furfuryl-Substituted Cyclohexylamines are Hydrogenated

R	R'	Yield, %	
		Octahydroindole alcohol	Tetrahydrofuran amine
H	H	18	62
C_2H_5	H	42	30
C_3H_7	H	70	—
H	CH_3	24	42
C_3H_7	CH_3	59	—


V R=H
VII R=CH_3
XIX R=H
XX R=CH_3


I R=R'=H
II R=C_2H_5, R'=H
III R=i-C_3H_7, R'=H
IX R=H, R'=CH_3
VIII R=i-C_3H_7, R'=CH_3
XVI R=R'=H
XVII R=C_2H_5, R'=H
XVIII R=i-C_3H_7, R'=H
XXIII R=H, R'=CH_3
XXIV R=i-C_3H_7, R'=CH_3


IV
XXI


VI
XXII

The products obtained were viscous liquids, difficult to separate by vacuum distillation. This made it

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*For Part I see [1].

Table 2

Alcohols of the Cyclopentanopyrrolidine and Octahydroindole Series and Related Compounds

Compound	Prepared from	Bp, °C (pressure, mm)	n_D^{20}	d_4^{20}	MR_D		Formula	Found, %			Calculated, %			Yield, %
					Found	Calculated		C	H	N	C	H	N	
XVI	I	151—154 (6)	1.5022	1.0135	53.38	53.72	$C_{11}H_{21}NO$	71.65 71.61	11.51 11.68	7.26 7.37	72.08	11.55	7.64	18.0
XVII	II	171—174 (9)	1.5003	0.9995	62.22	62.96	$C_{13}H_{25}NO$	73.38 73.50	12.29 12.07	6.62 6.82	73.93	11.85	6.63	43.0
XVIII	III	161—164 (5)	1.4990	0.9867	67.08	67.58	$C_{14}H_{27}NO$	75.02 75.19	12.12 12.42	6.03 6.37	74.73	12.10	6.23	70.0
XIX*	V	140—145 (5)	1.4990	—	—	—	$C_{10}H_{19}NO$	71.04 70.74	11.71 11.70	8.06 8.13	71.00	11.24	8.28	21.0
XX**	VII	133—135 (5)	1.4915	—	—	—	$C_{11}H_{21}NO$	71.33 71.46	11.45 11.46	7.14	72.08	11.55	7.64	8.0
XXI**	IV	189—191 (1)	1.5571	—	—	—	$C_{15}H_{21}NO$	77.64 77.47	9.10 9.42	6.38 6.27	77.92	9.09	6.06	22.0
XXII**	VI	173—177 (5)	1.5530	—	—	—	$C_{14}H_{25}NO$	76.90 76.90	9.03 9.13	5.98 5.98	77.42	8.75	6.45	13.0
XXIII	VIII	143—147 (7)	1.4941	0.9866	58.23	58.68	$C_{12}H_{23}NO$	73.10 73.34	11.81 11.85	7.43 7.35	73.05	11.77	7.11	24.0
XXIV	IX	158 (5)	1.4945	0.9701	71.90	72.53	$C_{15}H_{29}NO$	74.84 74.99	12.41 12.45	5.88 6.01	75.30	12.23	5.86	59.0

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*Mp 45°–47° C.

**Glassy mass.

Table 3

Tetrahydrofurfuryl-Substituted Cyclic Amines

Compound	Prepared from	Bp, ° C (pressure, mm)	n_D^{20}	d_4^{20}	MR_D		Formula	Found, %			Calculated, %			Yield, %
					Found	Calculated		C	H	N	C	H	N	
X	I	121—122(5)	1.4892	0.9875	53.66	53.76	$C_{11}H_{21}NO$	72.06 71.96	11.56 11.78	7.45 7.24	72.08	11.56	7.64	62.0
XI	II	127—129(5)	1.4892	0.9705	62.87	62.90	$C_{13}H_{25}NO$	74.15 74.65	11.99 11.92	7.06 6.93	74.00	11.94	6.64	30.0
XII	V	125—127(11)	1.4836	0.9980	48.49	49.04	$C_{10}H_{19}NO$	70.54 70.50	11.44 11.41	8.06 8.13	71.00	11.24	8.28	53.0
XIII	VII	123—125(15)	1.4789	0.9660	53.80	53.66	$C_{11}H_{21}NO$	71.89 71.88	11.39 11.31	7.72 7.46	72.08	11.55	7.64	56.0
XIV	IV	180—182(4)	1.5498	1.0820	68.12	68.53	$C_{15}H_{21}NO$	77.82	9.10	5.96 5.95	77.92	9.09	6.06	20.0
XV	VIII	132—136(10)	1.4864	0.9761	58.09	58.46	$C_{12}H_{23}NO$	72.94 72.95	11.34 11.30	6.85 7.10	73.05	11.77	7.11	42.0

Table 4

N, O-Diacetyl Derivatives of Alcohols of the Cyclopentanopyrrolidine and Octahydroindole and Other Systems

Compound	Prepared from	Bp, °C (pressure, mm)	n_D^{20}	Formula	Found, %			Calculated, %		
					C	H	N	C	H	N
XXXI	XVI	181—182 (2)	1.4870	$C_{15}H_{25}NO_3$	67.37 67.18	9.28 9.83	5.09 5.00	67.37	9.43	5.24
XXXII	XVII	179—180 (2)	1.4951	$C_{17}H_{29}NO_3$	68.72 68.71	10.18 9.80	5.12 4.70	69.15	9.82	4.75
XXXIII	XVIII	212—214 (5)	1.4970	$C_{18}H_{31}NO_3$	69.75 69.60	10.54 10.41	4.54 4.44	69.96	10.11	4.53
XXXIV	XIX	213—215 (2)	1.4860	$C_{14}H_{23}NO_3$	66.34 66.74	9.15 9.22	5.63 5.48	66.46	9.16	5.54
XXXV	XX	170—172 (4)	1.4830	$C_{15}H_{25}NO_3$	67.69	9.45	4.99 4.92	67.37	9.43	5.24
XXXVI*	XXI	198—200 (1)	—	$C_{19}H_{25}NO_3$	75.13 74.90	8.49 8.63	4.78 4.79	74.72	8.42	5.13
XXXVII*	XXII	239—242 (3)	—	$C_{18}H_{29}NO_3$	72.14 71.64	7.46 7.91	4.49 4.62	71.76	7.64	4.65
XXXVIII	XXIII	133—135 (5)	1.4765	$C_{14}H_{25}NO_2$	70.64 70.32	10.49 10.83	5.76 5.92	70.24	10.54	5.86
XXXIX	XXIV	133—134 (2)	1.4783	$C_{17}H_{31}NO_2$	72.02 71.85	11.50 11.37	4.86 5.37	72.30	11.08	4.97

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*Glassy mass.

Table 5

N-Acetyl Derivatives of Tetrahydrofuran Amines

Compound	Prepared from	Bp, °C (pressure, mm)	n_D^{20}	Formula	Found, %			Calculated, %		
					C	H	N	C	H	N
XXV*	X	171—175 (3,5)	—	$C_{13}H_{23}NO_2$	69.02 69.10	10.41 10.28	5.97 6.04	69.24	10.21	6.27
XXVI	XI	184 (6)	1.4989	$C_{15}H_{27}NO_2$	71.27 71.64	11.16 10.84	5.75 5.54	71.21	10.76	5.54
XXVII	XII	191—192 (4)	1.4960	$C_{12}H_{21}NO_2$	67.92 67.90	10.12 9.99	6.46 6.58	68.30	10.03	6.64
XXVIII	XIII	187—188 (7)	1.4930	$C_{13}H_{23}NO_2$	68.97 68.82	10.04 10.00	6.13 6.19	69.29	10.29	6.21
XXIX*	XIV	196—200 (3)	—	$C_{17}H_{23}NO_2$	75.13 74.90	8.49 8.63	4.78 4.79	74.72	8.42	5.13
XXX	XV	183—185 (6)	1.4982	$C_{14}H_{25}NO_2$	69.80 69.81	10.45 10.73	5.76 5.72	70.24	10.54	5.86

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*Glassy mass.

difficult to isolate them pure and caused considerable losses. Still it may be mentioned that cyclization to the condensed pyrrolidine system take place best of all with furfurylcyclohexylamines, and becomes difficult with bicyclic amines.

Since the problem in the present research was to investigate the sphere of application of the reaction, i.e., to apply it to the synthesis of polycyclic systems, no attention was paid to separating the mixtures of isomers obtained in a number of cases, it being intended to do this in the future.

Tables 2–5 give physical constants and analytical data for the compounds prepared and their derivatives.

The structures of the compounds synthesized were confirmed by preparing the N-acetyl and N,O-diacetyl derivatives, and observations on IR spectra.

In the region of N—H valence vibrations, the IR spectra of polycyclic alcohols show an absorption band frequency 3263–3270 cm^{-1}, while the tetrahydrofuran primary amines have two bands at 3325 and 3400 cm^{-1}. The acetyl derivatives of the tetrahydrofuran amines show an intense band at 1645–1665 cm^{-1}, corresponding to valence vibration of the carbonyl group of amides. The N,O-diacetyl derivatives of polycyclic pyrrolidinealkan-3-ols have, along with a 1645–1667 cm^{-1} band, an absorption band at 1750–1757 cm^{-1}, characteristic of the ester group.

EXPERIMENTAL*

The starting furan amines, 1-(α-furfuryl)-2-aminocyclohexane (I), 1-(α-furyl)-1-(1'-aminocyclohexyl-2')propane (II), 1-(α-furyl-1-(1'-aminocyclohexyl-2')-2-methylpropane (III), were prepared as previously described [4].

1-(α-furfuryl)-2-aminotetralin (IV), 1-(α-furfuryl)-2-aminocyclopentane (V), 1-(α-furfuryl)-2-aminoindane (VI), 1-(5'-methyl-2'-furfuryl)-2-aminocyclopentane (VII) were prepared by a somewhat modified method.

1-(α-furfuryl)-2-aminotetralin (IV). A 250 ml autoclave was filled with 25 g β-furfurylidene-α-tetralone [5], 125 ml MeOH saturated with NH_3, and 2.5 g Raney Ni. The initial hydrogen pressure was 65 atm, initial temperature 150° C. Reaction was complete in 14 hr. The products were filtered to remove catalyst, the MeOH and excess NH_3 distilled off under vacuum. To convert the amine in the residue salt, it was treated with dilute H_2SO_4 (1:10), and the non-nitrogen compounds were extracted with ether. Then solid alkali was added to the aqueous solution of the amine salt until the amine had completely separated out of the solution. It was separated off, and the water layer was extracted with ether. The ether extracts were combined with the amine, and the whole dried over solid KOH. The ether was distilled off, the residue vacuum distilled, taking a cut bp 165°–167° C (3 mm), yield 11.5 g (46%), d_4^{20} 1.0987; n_D^{20} 1.5680. Found: C 79.10; 78.84; H 7.46; 7.94; N 6.67; 6.53%, calculated for $C_{15}H_{17}NO$: C 79.29; H 7.49; N 6.17%. MR_D 67.60.

In a similar way β-furfurylidene-α-cyclopentanone [6] gave a 58% yield of amine V, bp 115° C (14 mm); d_4^{20} 1.0025; n_D^{20} 1.5010. Found: C 72.94; 72.92; H 9.24; 9.12; N 8.75; 8.67%; MR_D 48.60, calculated for $C_{10}H_{15}NO$: C 72.72; H 9.09; N 8.48%; MR_D 48.11. β-Furfurylidene-α-indanone [7] gave a 53% yield of amine VI, liquid bp 169°–171° C (10 mm); d_4^{20} 1.1135, n_D^{20} 1.5698. Found: C 78.84; 78.70; H 7.08; 6.92; N 6.54; 6.69%; MR_D 62.81, calculated for $C_{14}H_{15}NO$, C 78.84; H 7.09; N 6.5%; MR_D 62.98. 1-(5'-methyl-2'-furfuryl)pentan-2-one [7] gave a 55% yield of amine VII, liquid bp 120°–121° C (15 mm); d_4^{20} 1.0140; n_D^{20} 1.5025. Found: C 73.40; 73.28; H 9.55; 9.31; N 7.55; 7.42%; MR_D 52.21, calculated for $C_{11}H_{17}NO$: C 73.70; H 9.56; N 7.81%; MR_D 52.73.

SECONDARY FURAN AMINES (Typical Method).

1-(α-Furyl)-1-(1'-methylaminocyclohexyl-2')-2-methylpropane (VIII). A 610 ml rotating autoclave was filled with 58 g 1-(α-furyl)-1-(cyclohexan-1'-on-2'-yl)propane [3] and 180 ml MeOH containing 16 g $MeNH_2$ and 6 g Raney Ni. The initial hydrogen pressure was 120 atm, temperature 50° C. The reaction was complete in 8 hr, with absorption of the calculated amount of hydrogen. The products were filtered to remove the catalyst, and the MeOH and excess $MeNH_2$ were removed by vacuum distillation. The residue for conversion of the amine salt was brought to pH 4 with dilute HCl (1:2), then the neutral organic impurities extracted with ether. Then the aqueous amine salt solution was treated with solid caustic soda until the amine layer had separated from the solution completely. The amine was separated off and the aqueous layer was extracted with ether. The ether extracts were bulked with the amine, and the whole dried over solid KOH. The ether was distilled off, the residue vacuum distilled, taking a cut bp 125°–127° C (14 mm), which was 1-(α-tetrahydrofurfuryl)-2-aminocyclopentane (XII), yield 13.2 g (53%), after which the pressure was dropped to 5 mm, and at 140°–145° C 1-(cyclopentano[b]pyrrolidyl-2')propan-3-ol (XIX) came over, yield 5.2 g (21%).

The following were prepared similarly: 1-(α-tetrahydrofurfuryl)-2-aminocyclohexane (X), 1-(α-tetrahydrofurfuryl)-1-(1'-aminocyclohexyl-2')-propane (XI), 1-(5'-methyl-2'-tetrahydrofurfuryl)-2-aminocyclopentane (XIII), 1-(α-tetrahydrofurfuryl)-2-aminotetralin (XIV), 1-(α-tetrahydrofurfuryl)-2-methylaminocyclohexane (XV), and 1-(octahydroindolyl-2')-propan-3-ol (XVI), 1-(3'-ethyloctahydroindolyl-2')propan-3-ol (XVII), 1-(3'-isopropyloctahydroindolyl-2')-propan-3-ol (XVIII), 1-(cyclopentano[b]pyrrolidyl-2')butan-3-ol (XX), 1-(benzohexahydroindolyl-2')propan-3-ol (XXI), 1-(indanopyrrolidyl-2')propan-3-ol (XXII), 1-(benzohexahydroindolyl-2') propan-3-ol (XXIV), 1-(1'-methyl-3'-isopropyloctahydroindolyl-2')-propan-3-ol (XXIV).

N- and N,O-acetyl derivatives XXV-XXX and XXI-XXXIX were prepared as described in [8].

When amine V was hydrogenated (initial hydrogen pressure 90 atm), formation of compounds XII (49%) and XIX (10%) was accompanied by formation of 1-(1 -aminocyclopentyl-2')pentan-2,5-diol (XL) (21%). The aminodiol XL was a very viscous liquid, bp 196°–200° C (8 mm), n_D^{20} 1.5030. Found: C 64.57; 64.51; H 11.43; 11.18; N 7.37. 7.49%, calculated for $C_{10}H_{21}NO_2$: C 64.13. H 11.31: N 7.48%. N,O,O-triacetate of XL, glassy mass, bp 207°–210° C (3 mm). Found: C 61.83: H 9.09: N 4.61, 4.87%, calculated for $C_{16}H_{27}NO_5$: C 61.26: H 8.68: N 4.47%.

Hydrogenation of amine VII (initial hydrogen pressure 90 atm) gave 56% XIII, 8% XX, and 6% 1-(1'-cyclopentylamino-2')cyclohexan-2,5-diol (XLI), liquid bp 166°–169° (2 mm), n_D^{20} 1.4985. Found: C 65.28: 65.85: H 11.60: 11.50: N 6.88%, calculated for $C_{11}H_{23}NO_2$: C 65.67: H 11.40; N 6.96%.

N,O,O-Triacetyl derivative of XLI, liquid bp 218°–220° (4 mm), n_D^{20} 1.4785. Found: C 62.46: 62.53: H 9.23: 9.46: N 4.59: 4.57%, calculated for $C_{17}H_{29}NO_5$: C 62.45: H 8.93. N 4.28%.

The IR absorption spectra were determined by A. D. Peshekhonova with a twin-beam H-800 spectrometer, using NaCl prisms.

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Chernyshevskii Saratov State University