^{1}H Nmr Structural Analysis of Azabicyclospirohydantoins

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The structure and spatial conformation of 3-alkyl-3-azabicyclo[3.2.1]octane-8-spiro-5′-hydantoins and 8-alkyl-8-azabicyclo[4.3.1]decane-10-spiro-5-hydantoins has been determined on the basis of the data from ^{1}H nmr. The chair conformation of the piperidine ring and the presence of only one stereoisomer at the spiro carbon atom are corroborated. All these facts have been confirmed by x-ray diffraction methods (2).

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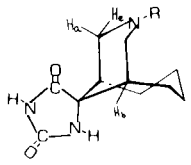
Introduction.

This paper reports the structural analysis of two new series of spirohydantoins, compounds **1-12**, listed in Table 1. The spirohydantoins have been obtained by the method previously reported (3).

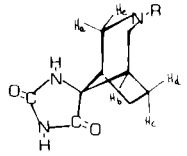
Table 1

8-Alkyl-8-azabicyclo[4.3.1]decane-10-spiro-5′-hydantoins



R	**1-6** Compound
-CH_3	**1**
-CH_2-CH_3	**2**
-CH_2-CH_2-CH_3	**3**
-i-C_3H_7	**4**
-CH_2-CH_2-CH_2-CH_3	**5**
-i-C_4H_9	**6**

3-Alkyl-3-azabicyclo[3.2.1]octane-8-spiro-5′-hydantoins

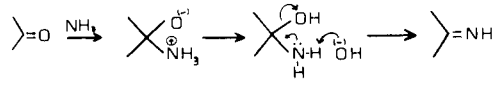


R	**7-12** Compound
-CH_3	**7**
-CH_2-CH_3	**8**
-CH_2-CH_2-CH_3	**9**
-i-C_3H_7	**10**
-CH_2-CH_2-CH_2-CH_3	**11**
-i-C_4H_9	**12**

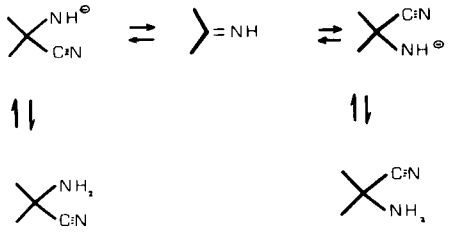
Results and Discussion.

According to Edward and Jitransgri (4) in studies of the Bucherer-Bergs reaction carried out on 4-methylcyclohexanone, the first step of this reaction begins with the partial transformation of the ketone in the ketimine by a probable sequence as shown in Scheme 1. From the reaction of the ketimine with the cyanide anion, Scheme 2, two epimeric aminonitriles are obtained. On mechanistic grounds it seems possible that the various equilibria shown in Scheme 2 are established quickly in alkaline solution. This assumption, receives some support from the observations of Tager and Christensen (5).

Scheme 1



Scheme 2



The mechanism shown in Scheme 3 is described by Bucherer and Steiner (6). In compound 5 of this Scheme, there is a steric hindrance because of the compression between the developing C=NH group and the hydrogen atoms of the polymethylene chain (mainly the C_3-H hydrogen) this confirms the fact that in the series **1-6** the α-isomer (Scheme 3) is the only one which is obtained.

In the other series, as can be seen in Figure 1, the same hindrance is repeated between the C=NH group and C_2 and C_4 axial hydrogen atoms, and therefore in the series **7-12** the β-isomer is the only one which is obtained. These assumptions are easily seen with a three dimensional model.

The ^{1}H nmr data for compounds **1-6** (Table 2) offers additional support for this conclusion; the δ values assigned to H_e are closely related to the δ value of H_e in *N,N*-dimethylbispidine of 2.62 ppm (7). On the other hand,

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Scheme 3

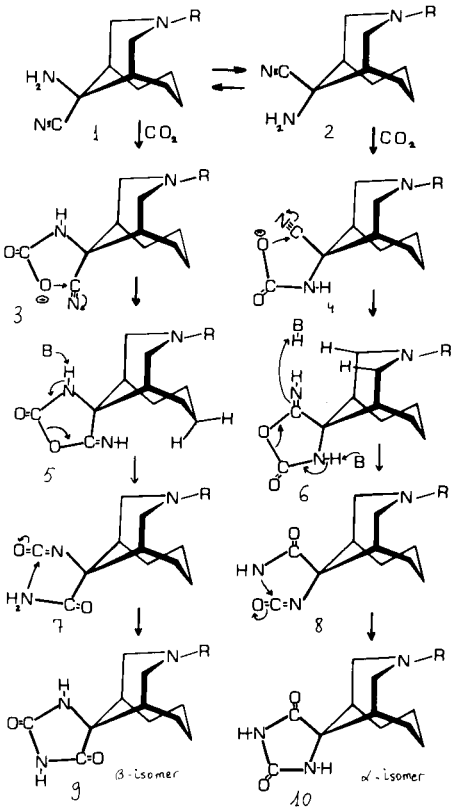


Figure 1

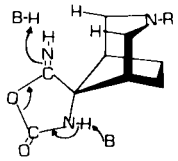


Figure 2

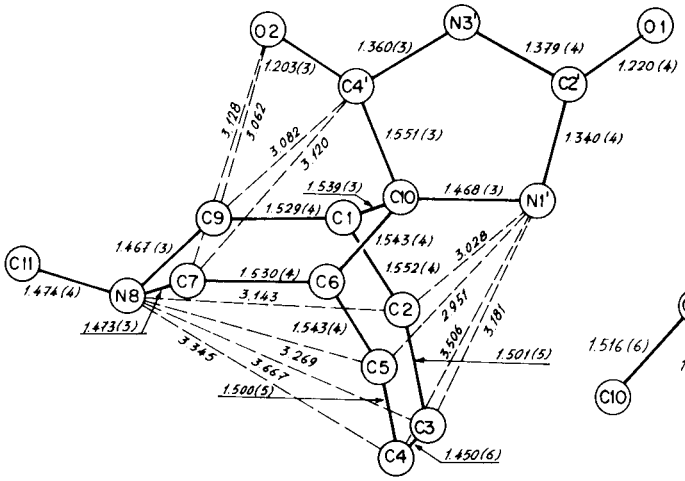


Figure 3

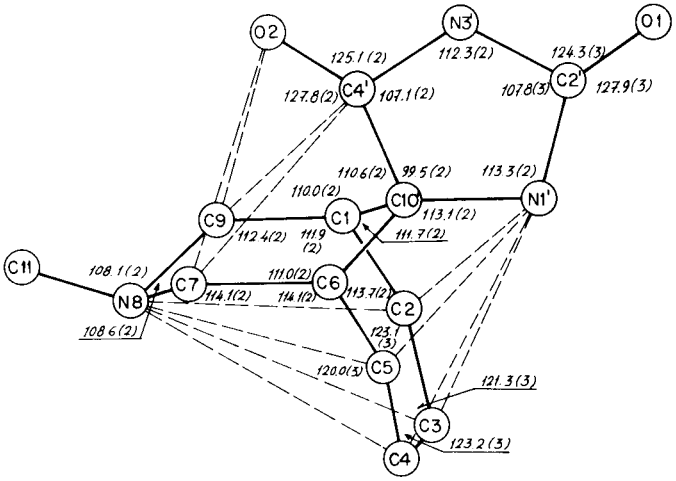


Figure 4

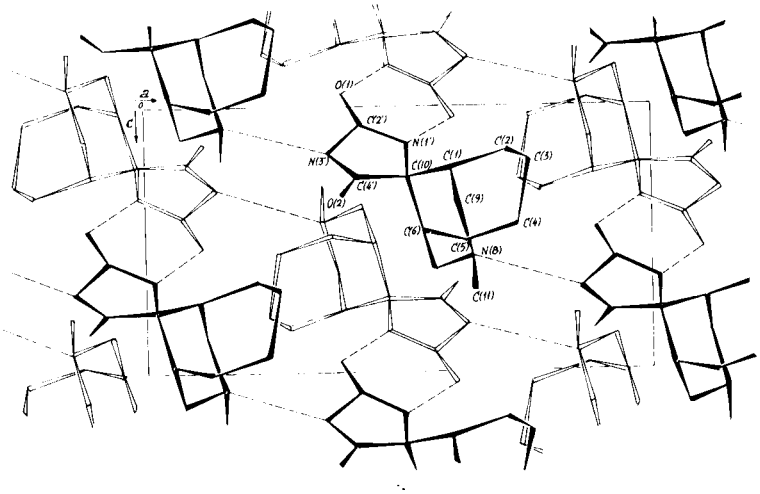


Figure 5

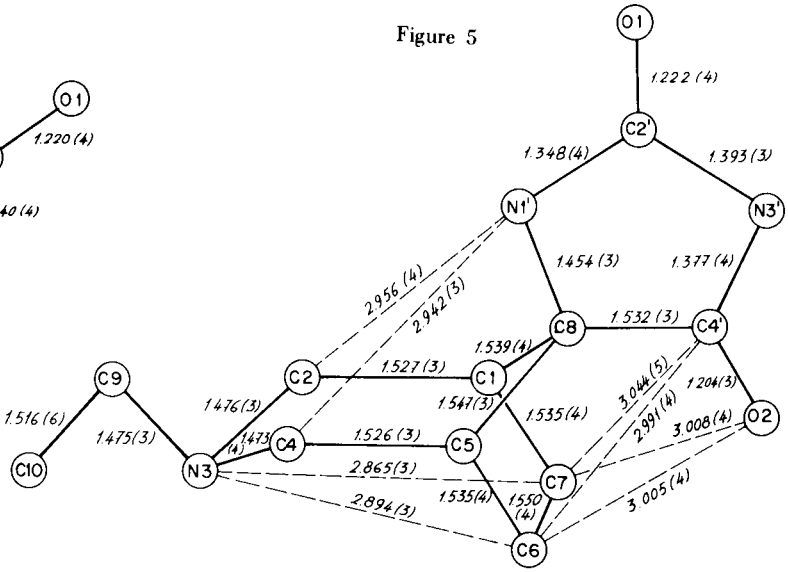


Figure 6

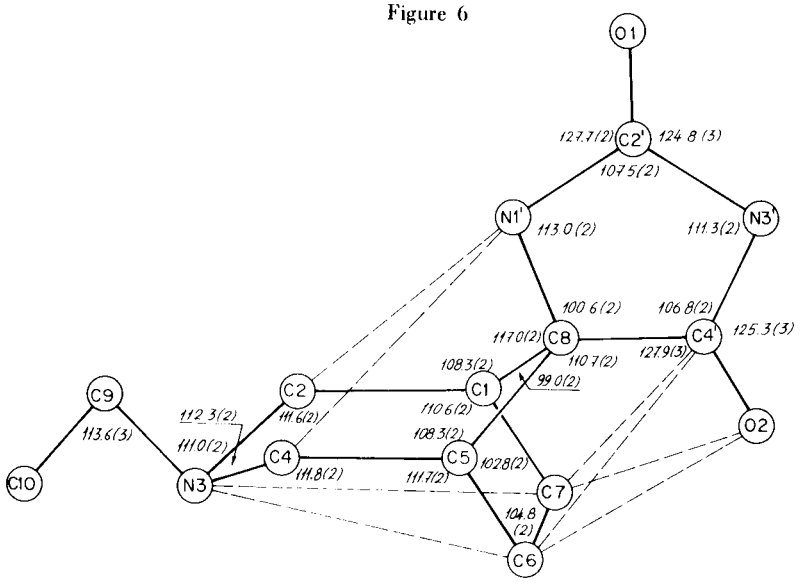
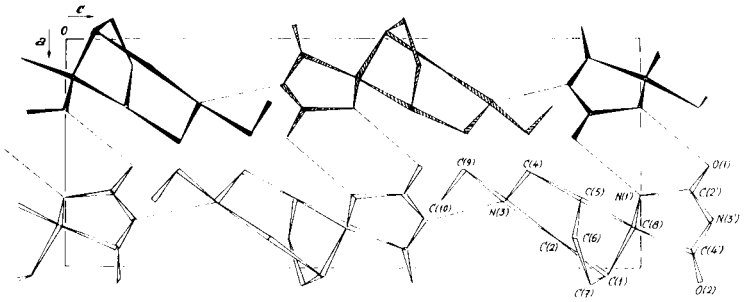


Figure 7



there is a difference between the δ value of H_a in *N,N*-dimethylbispidine (7) and the δ values of H_a in compounds **1-6**. This difference of about 0.8 ppm is produced by the field effect due to the magnetic anisotropy of the $C'_4=O$ group.

The chair conformation of the piperidine ring is corroborated by the values of the coupling constants JH_a-H_b and JH_e-H_b of approximately 3 H_Z (Table 3). In compounds **1-6**, JH_a-H_b is greater than JH_e-H_b (Table 3); therefore, the dihedral angle H_e-C-C-H_b is larger than H_a-C-C-H_b. Consequently, the chair conformation of the pipridine ring is partially flattened, which is probably due to the steric hindrance of the polymethylene chain. This difference between JH_a-H_b and JH_e-H_b is increased in the

Table 2

Chemical Shifts of Compounds **1-6** in Deuteriochloroform (δ Values, TMS as Internal Reference)

	1	**2**	**3**	**4**	**5**	**6**	**1** Hydrochloride (a)
H_{7a}, H_{9a}	2.91	3.07	3	3.4	3	3	3.92
H_{7e}, H_{9e}	2.45	2.55	2.5	2.6	2.52	2.51	3.48
H_1, H_6	2.06	2.1	2.06	2.16	2.06	2.01	2.6
H_2, H_5	1.8	2	1.64	1.9	1.82	1.82	1.8
H_3, H_4	1.8	2	1.64	1.9	1.8	1.8	1.8
$N^{1'}$-H	6.08	6.3	6.1	6.2	6.16	5.85	
$N^{3'}$-H	8.8	9.2	8.8	8.3	8.94	8.25	
-CHα	2.22	2.37	2.26	2.3	2.29	2.1	2.97
-CHβ		1.05	1.46	1.05	1.46	2.24	
-CHγ			0.9		1.3	0.9	
-CHδ					0.9		

(a) In deuterium oxide.

Table 3

Coupling Constants of Compounds **1-6** in Deuteriochloroform (Hz Values, TMS as Internal Reference)

	1	**2**	**3**	**4**	**5**	**6**	**1** Hydrochloride (a)
JHa-He	12	12	12.2	11.3	12.8	11.5	13
JHa-Hb	3.2	3.3	3.2	2.6	2.6	3	5
JHe-Hb	1	1	1	1	1	1	1
JHα-Hβ		6	6	7	7	7	
JHβ-Hγ			6		7	7	
JHγ-Hδ					7		

(a) In deuterium oxide.

Table 4

Chemical Shifts of Compounds **7-8** Hydrochlorides in Deuterium Oxide (δ Values, TMS as Internal Reference)

Chemical Shifts of Compounds **9-12** in Dimethylsulfoxide (δ Values, TMS as Internal Reference)

	7 Hydrochloride (a)	**8** Hydrochloride (a)	**9**	**10**	**11**	**12**
Ha	3.28	3.24	2.47	2.46	2.47	2.47
He	3.53	3.42	2.47	2.46	2.47	2.47
Hb	2.54	2.24	1.92	1.96	1.95	1.92
Hc	2.48	2.35	1.92	1.96	1.95	1.92
Hd	1.85	1.96	1.60	1.56	1.59	1.65
$N^{1'}$-H			5.63	8.2	5.66	5.62
$N^{3'}$-H			8.12	10.4	8.12	8
CHα	2.93	3.1	2.32	2.66	2.34	2.10
CHβ		1.23	1.38	0.98	1.32	1.65
CHγ			0.84		1.32	0.85
CHδ					0.86	

(a) In deuterium oxide.

Table 5

N-Alkyl-8-azabicyclo[4.3.1]decane-10-spiro-5′-hydantoins and *N*-Alkyl-3-azabicyclo[3.2.1]octane-8-spiro-5′-hydantoins

Compounds	M.p.°C	Ir (C=O) (cm^{-1}) (a)	Ms m/e	Yield % (b)	Formula	Analysis					
						Calculated			Found		
						C	H	N	C	H	N
1	340	1695	237	84	$C_{12}H_{19}N_3O_2$	60.73	8.07	17.71	60.94	7.83	17.90
2	230	1760, 1720, 1695	251	8.3	$C_{13}H_{21}N_3O_2$	62.12	8.41	16.71	61.93	8.65	16.40
3	222	1760, 1715, 1690	265	14.15	$C_{14}H_{23}N_3O_2$	63.36	8.74	15.83	63.47	8.92	15.67
4	248	1760, 1715, 1695	265	25.15	$C_{14}H_{23}N_3O_2$	63.36	8.74	15.83	63.48	8.69	15.98
5	186	1760, 1720, 1690	279	31.39	$C_{15}H_{25}N_3O_2$	64.48	9.02	15.03	64.27	9.38	14.87
6	220	1760, 1720, 1690	279	23	$C_{15}H_{25}N_3O_2$	64.48	9.03	15.03	64.69	9.23	15.38
7	340	1760, 1720, 1790	209	84	$C_{10}H_{15}N_3O_2$	57.40	7.22	20.08	57.26	7.46	19.79
8	240	1760, 1720, 1690	223	73	$C_{11}H_{17}N_3O_2$	59.17	7.67	18.82	59.35	7.74	18.57
9	252	1760, 1720, 1690	237	46	$C_{12}H_{19}N_3O_2$	60.73	8.07	17.71	60.58	8.15	17.43
10	259	1760, 1720, 1690	237	88	$C_{12}H_{19}N_3O_2$	60.73	8.07	17.71	60.45	7.76	17.31
11	207	1760, 1720, 1690	251	53	$C_{13}H_{21}N_3O_2$	62.12	8.42	16.72	61.96	8.28	17.02
12	215	1760, 1720, 1690	251	50	$C_{13}H_{21}N_3O_2$	62.12	8.42	16.72	62.36	8.24	16.52

(a) Potassium bromide. (b) From ethanol.

hydrochloride of compound **1** (Table 3). Therefore, the sustitution of the axial lone pair of the piperidine nitrogen atom by a hydrogen atom produces a greater steric hindrance.

Finally, the results obtained by x-ray diffraction from compound **1** (2) are in good agreement with all of the conclusions reached above. From the x-ray diffraction studies (2) it has been deduced that: (a) The cycloheptane ring

has a completely distorted chair conformation. (b) The piperidine ring is partially flattened. These two facts are due to the steric hindrance produced by the hydantoin ring. For the β-isomer, the steric hindrance would be great enough so as to make it impossible to form. (c) The piperidine nitogen atom has a pyramidal geometry and the *N*-methyl group attached to it is in an equatorial position. It is interesting to note that in the crystalline state of compound **1**, there are two types of hydrogen bonds: one between the imide nitrogen and the piperidine nitrogen atom, the other one between the C′$_2$=O oxygen atom and the amide nitrogen atom. The interatomic distances, valence angles and the packing of the molecules in the unit cell of compound **1** are shown in Figures 2,3 and 4, respectively.

The ^{1}H nmr data of spirohydantoins **7-12** show that the Bucherer-Bergs synthesis yields only the β-isomer. The ^{1}H nmr spectra of compounds **7** and **8** as hydrochlorides were obtained in deuterium oxide, the ^{1}H nmr spectra of compounds **9-12** were obtained in DMSO because of solubility problems. By considering δ values in compounds **7-12** (Table 4), the difference between the δ values assigned to H_c and H_d can be attributed only to the field effect due to the magnetic anisotropy of the C′$_4$=O group. The JH_e-H_b values of approximately 3 Hz confirms the chair conformation for the piperidine ring.

The results obtained by x-ray diffraction of compound **8** are in very good agreement with ^{1}H nmr conclusions. From the x-ray diffraction studies (2) it has been deduced that: (a) The cyclopentane ring shows a slightly distorted envelope conformation. (b) The piperidine ring shows a distorted chair conformation. (c) The piperidine nitrogen atom shows a pyramidal geometry and the ethyl group attached to it is in an equatorial position. Also in the crystalline state of compound **8**, there are two types of hydrogen bonds, quite similar to those found in compound **1**. The interatomic distances, valence angles and the packing of the molecules in the unit cell of compound **8** are shown in Figures 5, 6 and 7, respectively. In the ^{1}H nmr spectra of compounds **1-12**, the clearness of the signals are incompatible with the presence of two stereoisomers.

There is a complete agreement between the proposed mechanistic hypothesis and the experimental facts for compounds **1-6** and **7-12**; however, there is not such agreement in the 3-alkyl-3-azabicyclo[3.3.1]nonane-9-spiro-5′-hydantoins reported previously (3), where only one isomer appears instead of the two which would be expected. This question is now being studied.

EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined using a Perkin-Elmer 577 Spectrophotometer. The ^{1}H nmr spectra have been recorded using a Varian XL 100 Spectrometer. The mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6M Spectrometer. The spirohydantoins have been obtained by the method previously reported (3) from the corresponding azabicyclanones (8). The newly synthesized spirohydantoins are described in Table 5.

Acknowledgment.

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REFERENCES AND NOTES

(1) Author to whom correspondence should be addressed.

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