Conformational and Configurational Studies on 3-Azabicyclo[3.3.1]nonane (3-ABN) Derivatives and Related Systems Employing Carbon-13 NMR Spectroscopy

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The ^{13}C nmr spectra of 4 *cis*-2,4-diphenyl-3-azabicyclo[3.3.1]nonanes, 11 *cis*-2,4-diaryl-3-azabicyclo[3.3.1]-nonan-9-ones, 26 *cis*-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ols or acetates thereof, 5 *cis*-2,4-diaryl-3-azabicyclo[4.3.1]decan-10-ones or -10-ols and 5 *cis*-2,4-diphenyl-3-aza-7-thiabicyclo[3.3.1]nonan-9-ones, -9-ols or 9-yl acetates have been recorded. Except for the 7-thia compounds, which appear to exist mainly in the configuration and conformation with the nitrogen-containing ring in the boat form, these compounds seem to exist overwhelmingly in chair-chair conformations. The configuration of the 9-ols and their acetates (*syn* or *anti* to the nitrogen-containing ring) has been deduced from the spectra. In a number of cases, the structures assigned differ from those earlier postulated. Broadening of one set of aryl signals (probably those due to the *ortho* carbons) in the case of *N*-methyl (but not N-H) compounds without *ortho* substituents is ascribed to restricted phenyl rotation.

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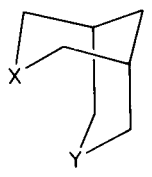
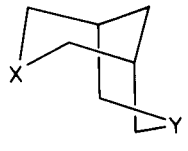
Bicyclo[3.3.1]nonanes (BCNs, I) with simple substituents prefer to adopt chair-chair conformations (Ia) with slight



Ia

X = Y = CH_2 (BCN)



Ib

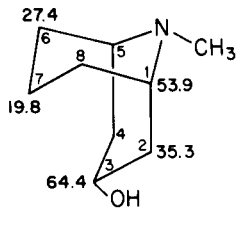
X = Y = CH_2 (BCN)

II X = NH, Y = CH_2 (3-ABN)
III X = Y = NH (3,7-DABN)
IV X = NH, Y = S (7-T-3ABN)
V X = NH, Y = O (7-O-3ABN)

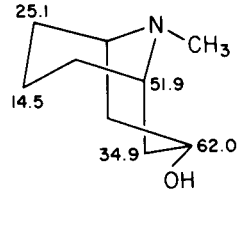
ring flattening (1-4) while those with bulky substituents at 3 or 7 *endo* positions exist in chair-boat conformations (Ib) (5-7). In the heterocyclic analogs (8) of BCN, bicyclo[3.3.1]-nonane (9), the possibility of the heterocyclic ring acquiring the boat form is enhanced since some of the interactions present in the boat form of cyclohexane may be diminished; in addition there may be attractive intramolecular steric and/or polar interactions between the heteroatoms and the substituent. The conformational analysis of derivatives of 3-azabicyclo[3.3.1]nonane (II) (10), 3,7-diazabicyclo[3.3.1]nonane (III), 7-thia-3-azabicyclo[3.3.1]nonane (IV) (11) and 7-oxa-3-azabicyclo[3.3.1]-nonane (V) (12,13) (indicated in this paper as 3-ABN, 3,7-DABN,7-T-3-ABN and 7-O-3-ABN, respectively) has, in the past, been undertaken with the aid of ir (14,15) and proton nmr (16-18) spectroscopy, kinetic methods (19,20) and by the use of dipole moment calculations (21,22) in addition to the unequivocal X-ray crystallographic technique (13,23-25). Also, semiempirical calculations (26) have been performed; they indicate the parent compound III to be in the double chair form. In this paper we report configurational and conformational assignments to several 2,4-diaryl-3-ABN's, 2,4-diaryl-7-hetero-3-ABN's and their 9-keto and 9-hydroxy derivatives employing ^{13}C nmr spectroscopy.

^{13}C nmr spectroscopy has proved to be an excellent tool in stereochemical studies (26,27). Particularly useful for configurational and conformational assignment in cyclohexanes and saturated heterocyclic analogs is the upfield

Scheme 1 (32)

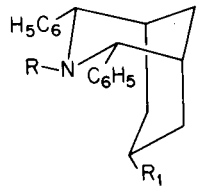


VIa



VIb

Table 1



IX

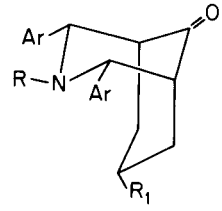
a R = R$_1$ = H
b R = CH$_3$, R$_1$ = H
c R = H, R$_1$ = (CH$_3$)$_3$C
d R = CH$_3$, R$_1$ = (CH$_3$)$_3$C

^{13}C NMR Spectral Data on 2,4-Diphenyl-3-azabicyclo[3.3.1]nonanes (IX)

									Aromatic Carbons				
No.	R	R$_1$	C(1,5)	C(2,4)	C(6,8)	C(7)	C(9)	*N*-Me	*ipso*	*ortho*	*meta*	*para*	Other carbons
IX	H	H	35.2$_3$	65.4$_3$	26.1$_6$	22.1$_5$	37.2$_6$		145.4$_1$	126.8$_5$	128.1$_0$	126.5$_7$	
IXb	Me	H	36.7$_5$	74.3$_9$	26.5$_9$	21.6$_2$	36.5$_7$	44.5$_7$	144.2$_6$	127.5$_1$(a)	128.0$_1$	126.2$_7$	
IXc	H	*t*-Bu	35.9$_1$	65.2$_5$	26.9$_2$	41.2$_5$	37.1$_1$		145.4$_3$	126.9$_5$	128.0$_7$	126.6$_6$	32.7$_4$ (Cq), 26.9$_2$ (Me)
IXd	Me	*t*-Bu	37.3$_7$	74.2$_3$	26.9$_6$	40.6$_8$	36.4$_8$	44.4$_1$	144.3$_0$	128.0$_0$(a)	128.0$_0$	126.4$_1$	32.5$_5$ (Cq), 27.3$_8$ (Me)

(a) Broad signal.

Table 2



X

X

a R = R$_1$ = H, Ar = C$_6$H$_5$
b R = CH$_3$, R$_1$ = H, Ar = C$_6$H$_5$
c R = R$_1$ = H, Ar = *o*-CH$_3$C$_6$H$_4$
d R = R$_1$ = H, Ar = *p*-CH$_3$C$_6$H$_4$
e R = R$_1$ = H, Ar = *o*-CH$_3$OC$_6$H$_4$
f R = R$_1$ = H, Ar = *p*-CH$_3$OC$_6$H$_4$
g R = H, R$_1$ = (CH$_3$)$_3$C, Ar = C$_6$H$_5$
h R = R$_1$ = H, Ar = *p*-ClC$_6$H$_4$
i R = CH$_3$, R$_1$ = H, Ar = *p*-CH$_3$C$_6$H$_4$
j R = CH$_3$, R$_1$ = H, Ar = *o*-ClC$_6$H$_4$
k R = CH$_3$, R$_1$ = H, Ar = *o*-CH$_3$OC$_6$H$_4$

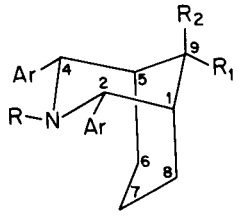
^{13}C NMR Spectral Data on 2,4-Diaryl-3-azabicyclo[3.3.1]nonan-9-ones (X)

										Aromatic Carbons					
No.	R	X (a)	Y (b)	R$_1$	C(1,5)	C(2,4)	C(6,8)	C(7)	C(9)	*N*-Me	*ipso*	*ortho*	*meta*	*para*	*meta'*	*ortho'*	Other carbons
Xa	H	H	H	H	54.0$_5$	64.8$_4$	29.0$_8$	21.2$_0$	217.2$_0$		141.3$_7$	126.9$_1$	128.5$_7$	127.5$_7$			
Xb	Me	H	H	H	54.6$_4$	74.4$_7$	29.6$_5$	20.7$_5$	216.9$_3$	43.4$_8$	140.7$_1$	127.3$_2$(c)	128.5$_4$	127.6$_9$			
Xc	H	Me	H	H	50.7$_1$	61.3$_2$	29.2$_4$	21.0$_1$	217.5$_5$		139.0$_1$	134.7$_4$	130.7$_9$	(127.1$_4$)	125.9$_2$	(127.1$_4$)	19.0$_2$ (ArMe)
Xd	H	H	Me	H	54.1$_1$	64.6$_0$	29.0$_5$	21.1$_6$	217.5$_6$		(138.4$_2$)	126.7$_7$	129.1$_8$	(137.0$_6$)			21.1$_0$ (ArMe)
Xe	H	OMe	H	H	50.2$_9$	58.0$_6$	29.9$_6$	20.9$_2$	218.9$_9$		129.6$_7$	156.1$_5$	110.1$_9$	(128.0$_7$)	120.2$_6$	(127.7$_0$)	55.1$_1$ (ArOMe)
Xf	H	H	OMe	H	54.2$_1$	64.3$_3$	28.9$_9$	21.1$_9$	217.6$_5$		133.4$_9$	127.9$_2$	113.8$_7$	158.9$_8$			55.2$_2$ (ArOMe)
Xg	H	H	H	*t*-Bu	53.7$_0$	64.7$_6$	29.9$_6$	40.6$_0$	217.9$_0$		141.3$_6$	127.0$_2$	128.5$_4$	127.4$_7$			
Xh	H	H	Cl	H	53.7$_8$	64.2$_1$	28.9$_4$	21.1$_7$	215.9$_6$		139.6$_5$	(128.6$_5$)	(128.1$_6$)	133.5$_0$			
Xi	Me	H	Me	H	54.8$_7$	74.4$_4$	29.7$_2$	21.0$_5$	216.9$_3$	43.4$_3$	(137.8$_9$)	127.6$_7$	129.2$_2$	(136.8$_5$)			20.8$_1$ (ArMe)
Xj	Me	Cl	H	H	61.0$_1$	75.7$_4$	29.5$_4$	20.9$_0$	215.7$_2$	49.6$_5$	138.2$_3$	132.6$_9$	(130.0$_9$)	(128.7$_8$)	126.7$_9$	(128.6$_4$)	
Xk	Me	OMe	H	H	50.9$_2$	66.8$_4$	30.6$_1$	20.5$_4$	218.1$_1$	43.4$_9$	128.7$_7$	156.6$_4$	110.8$_3$	(128.9$_8$)	120.3$_1$	(127.7$_8$)	55.2$_5$ (ArOMe)

(a) *ortho*-Substituent in Ar. (b) *para*-Substituent in Ar. (c) Broad signal.

shifting γ-gauche effect (27,29,30). ^{13}C nmr has also been used in conformational studies in the BCN system (31,32) although, as shown in Scheme 1, the crucial difference between chair-chair and chair-boat systems may give rise to but minor changes in shift except at C(7) (32), with the chair-boat system showing the upfield shifts.

Table 3



XIII

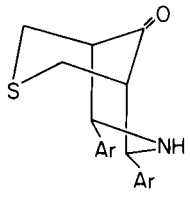
a R = R$_1$ = H, R$_2$ = OH, Ar = C$_6$H$_5$
b R = R$_2$ = H, R$_1$ = OH, Ar = C$_6$H$_5$
c R = CH$_3$, R$_1$ = H, R$_2$ = OH, Ar = C$_6$H$_5$
d R = CH$_3$, R$_1$ = OH, R$_2$ = H, Ar = C$_6$H$_5$
e R = R$_1$ = H, R$_2$ = OH, Ar = *o*-CH$_3$C$_6$H$_4$
f R = R$_2$ = H, R$_1$ = OH, Ar = *o*-CH$_3$C$_6$H$_4$
g R = CH$_3$, R$_1$ = OH, R$_2$ = H, Ar = *o*-CH$_3$C$_6$H$_4$
h R = R$_1$ = H, R$_2$ = OH, Ar = *p*-CH$_3$C$_6$H$_4$
i R = R$_2$ = H, R$_1$ = OH, Ar = *p*-CH$_3$C$_6$H$_4$
j R = CH$_3$, R$_1$ = OH, R$_2$ = H, Ar = C$_6$H$_5$
k R = R$_1$ = H, R$_2$ = OH, Ar = *o*-CH$_3$OC$_6$H$_4$
l R = CH$_3$, R$_1$ = H, R$_2$ = OH, Ar = *o*-CH$_3$OC$_6$H$_4$
m R = R$_1$ = H, R$_2$ = OH, Ar = *p*-CH$_3$OC$_6$H$_4$
n R = R$_2$ = H, R$_1$ = OH, Ar = *p*-CH$_3$OC$_6$H$_4$
o R = R$_1$ = H, R$_2$ = OH, Ar = *o*-ClC$_6$H$_4$
p R = CH$_3$, R$_1$ = H, R$_2$ = OH, Ar = *o*-ClC$_6$H$_4$
q R = R$_1$ = H, R$_2$ = OH, Ar = *p*-ClC$_6$H$_4$
r R = H, R$_1$ = OH, R$_2$ = C$_6$H$_5$, Ar = C$_6$H$_5$
s R = H, R$_1$ = C$_6$H$_5$, R$_2$ = OH, Ar = C$_6$H$_5$
t R = CH$_3$, R$_1$ = C$_6$H$_5$, R$_2$ = OH, Ar = C$_6$H$_5$
u R = H, R$_1$ = CH$_3$, R$_2$ = OH, Ar = *p*-CH$_3$OC$_6$H$_4$
v R = H, R$_1$ = C$_6$H$_5$, R$_2$ = OH, Ar = *p*-CH$_3$OC$_6$H$_4$
w R = CH$_3$, R$_1$ = OAc, R$_2$ = H, Ar = C$_6$H$_5$
x R = CH$_3$, R$_1$ = OAc, R$_2$ = H, Ar = *o*-CH$_3$C$_6$H$_4$
y R = CH$_3$, R$_1$ = OAc, R$_2$ = H, Ar = *o*-CH$_3$C$_6$H$_4$
z R = CH$_3$, R$_1$ = OAc, R$_2$ = H, Ar = *p*-CH$_3$C$_6$H$_4$

^{13}C NMR Spectral Data on 2,4-Diaryl-3-azabicyclo[3.3.1]nonan-9-ols and Derivatives (XIII)

												Aromatic Carbons						Others
Cpd.	R	X (a)	Y (b)	R$_1$	R$_2$	C(1,5)	C(2,4)	C(6,8)	C(7)	C(9)	*N*-Me	*ipso*	*ortho*	*meta*	*para*	*meta'*	*ortho'*	Me or OMe
XIIIa	H	H	H	H	OH	42.13	57.86	26.30	21.18	74.12		144.71	126.85	128.14	126.59			
XIIIb	H	H	H	OH	H	41.64	64.02	19.37	20.99	74.55		143.90	126.90	128.29	126.90			
XIIIc	Me	H	H	H	OH	43.53	66.82	26.66	20.62	73.38	44.01	143.59	127.76(c)	128.14	126.39			
XIIId	Me	H	H	OH	H	42.95	73.65	19.69	20.57	74.52	44.15	143.09	127.69(c)	128.24	126.66			
XIIIe	H	Me	H	H	OH	38.52	54.65	26.56	21.01	74.26		142.28	137.58	130.32	(126.74)	125.74	(127.23)	19.09
XIIIf	H	Me	H	OH	H	37.86	60.53	19.52	20.74	74.52		141.42	134.62	130.50	(126.53)	125.82	(127.10)	19.15
XIIIg	Me	Me	H	OH	H	39.11	69.27	19.17	20.39	73.86	43.92	140.29	134.84	130.66	(126.15)	125.68	(127.96)	19.88
XIIIh	H	H	Me	H	OH	42.21	57.71	26.47	21.19	74.26		(136.04)	126.79	128.84	(141.71)			21.05
XIIIi	H	H	Me	OH	H	41.60	63.73	19.36	20.99	74.51		(136.29)	126.71	128.87	(140.92)			21.14
XIIIj	Me	H	Me	OH	H	42.95	73.39	19.71	20.57	73.64	44.02	(136.00)	127.58(c)	128.86	(140.10)			21.07
XIIIk	H	OMe	H	H	OH	38.15	51.73	26.97	20.75	74.24		132.97	156.30	110.06	(127.90)	120.32	(127.18)	55.35
XIIIℓ	Me	OMe	H	H	OH	39.16	59.52	27.36	20.35	73.31	43.90	131.34	156.73	110.55	(128.95)	120.23	(126.84)	55.33
XIIIm	H	H	OMe	H	OH	42.18	57.36	26.32	21.24	74.14		136.11	127.78	113.57	158.44			55.19
XIIIn	H	H	OMe	OH	H	41.65	63.40	19.43	21.04	74.34		136.11	127.78	113.57	158.44			55.19
XIIIo	H	Cl	H	H	OH	37.49	54.90	26.39	20.77	73.73		141.37	132.45	(129.63)	(127.76)	126.57	(128.90)	
XIIIp	Me	Cl	H	H	OH	36.99	60.42	26.41	20.54	73.49	-(d)	140.46	132.48	(129.71)	(127.97)	126.59	(128.77)	
XIIIq	H	H	Cl	H	OH	41.98	57.31	26.08	21.55	73.78		142.98	(128.35)	(128.18)	132.25			
XIIIr	H	H	H	OH	Ph	42.39	60.72	20.99	19.99	75.14		144.39	128.17	126.60	125.75	(Ar at C 2,4)		
												144.27	126.74	129.33	127.79	(Ar at C 9)		
XIIIs	H	H	H	Ph	OH	42.88	58.73	23.64	20.67	75.77		145.13	127.06	128.17	128.92	(Ar at C 2,4)		
												144.17	125.36	126.63	127.58	(Ar at C 9)		
XIIIt	Me	H	H	Ph	OH	44.24	68.00	23.99	20.29	75.14		144.10	128.70(c)	126.46	128.70	(Ar at C 2,4)		
												143.97	127.63	128.97	125.12	(Ar at C 9)		
XIIIu	H	H	OMe	Me	OH	46.38	58.09	23.51	20.39	73.52		137.34	127.80	113.51	158.30			55.22, 28.45 (C9)
XIIIv	H	H	OMe	Ph	OH	42.95	58.28	23.67	20.76	75.76		137.25	128.06	113.62	158.32			55.27
XIIIw	Me	H	H	H	OAc	40.70	67.71	26.55	20.58	76.12	44.10	143.10	127.79	128.23	126.63			170.25 (CO) 21.48 (Me)
XIIIx	Me	Me	H	H	OAc	36.95	63.57	26.74	20.49	76.44	43.90	140.27	134.85	130.70	(126.15)	(125.72)	(128.02)	170.27, 21.31 (Ac) 18.86 (ArMe)
XIIIy	Me	Me	H	OAc	H	36.62	68.98	19.22	20.28	75.73	43.84	139.93	135.06	130.74	(126.29)	(125.69)	(127.94)	170.57, 21.34 (Ac) 20.60 (ArMe)
XIIIz	Me	H	Me	OAc	H	40.14	72.91	20.44	20.44	75.90	43.94	(136.16)	128.90	127.65	(139.68)			170.45, 21.34 (Ac) 21.09 (ArMe)

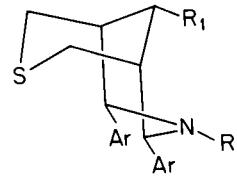
(a) *ortho*-Substituent in aryl group. (b) *para*-Substituent in aryl group. (c) Broadened signal. (d) Not recorded.

Table 4



XI

a Ar = C_6H_5
b Ar = p-ClC_6H_4



XIV

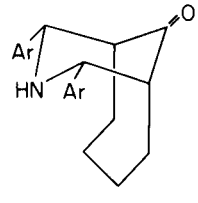
a R = H, R_1 = OH
b R = CH_3, R_1 = OH
c R = CH_3, R_1 = OAc

^{13}C NMR Spectral Data on 7-Thia-3-azabicyclo[3.3.1]nonane Derivatives (XI, XIV)

										Aromatic carbons			
No.	R	X (a)	Y (b)	R_1	C(1,5)	C(2,4)	C(6,8)	C(9)	*N*-Me	*ipso*	*ortho*	*meta*	*para*
XIa	H	H	H	=O	55.0_6	63.5_8	37.4_4	212.7_8		144.6_8	127.0_7	128.7_8	127.9_9
XIb	H	H	Cl	=O	54.9_4	62.8_8	37.3_4	211.9_6		142.9_4	128.4_1	129.0_5	129.0_1
XIVa	H	H	H	OH	42.3_8	62.1_4	34.1_7	73.7_1		144.4_6	127.7_1	128.7_7	127.6_0
XIVb	Me	H	H	OH	44.6_3	71.1_7	33.5_3	72.5_5	47.0_0	145.0_6	128.4_4	128.7_9	127.3_1
XIVc	Me	H	H	OAc	55.3	65.5	35.9	75.8		156.7_3	127.7_3	128.7_3	127.5_1

(a) *ortho*-Substituent in Ar. (b) *para*-Substituent in Ar.

Table 5



XII

a Ar = C_6H_5
b Ar = o-ClC_6H_4
c Ar = o-$CH_3C_6H_4$
d Ar = p-$CH_3C_6H_4$

^{13}C NMR Spectral Data on 2,4-Diaryl-3-azabicyclo[4.3.1]decane Derivatives (XII, XV)

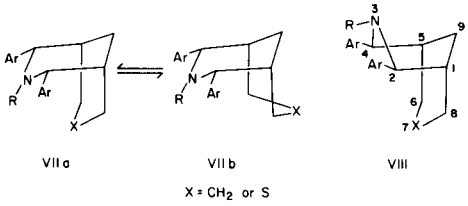
										Aromatic carbons					
No.	X (a)	Y (b)	R_1		R_2	C(1,5)	C(2,4)	C(6,9)	C(7,8)	C(10)	*ipso*	*ortho*	*meta*	*para*	*meta'* *ortho'*	Other carbons
XIIa	H	H		=O		55.0_3	63.7_2	25.9_9	24.1_4	214.0_2	140.9_4	126.6_7	128.5_3	127.3_3		
XIIb	Cl	H		=O		50.4_9	60.2_8	26.1_0	24.4_7	212.7_3	138.0_5	132.6_8	$(129.9_4)(128.6_1)$	126.7_7	(128.6_0)	
XIIc	Me	H		=O		51.8_0	60.6_7	26.0_8	24.2_4	214.4_3	138.7_9	134.7_8	130.6_5	(126.9_7)	125.9_1 (127.0_5)	19.1_7 (ArMe)
XIId	H	Me		=O		55.0_7	63.4_9	26.0_2	24.1_6	214.4_4	(136.8_3)	126.5_4	129.1_7	(137.9_5)		
XV (c)	Cl	H	H		OH	39.4_9	61.4_5	27.2_0	25.1_3	77.4_1	140.1_8	132.5_9	$(129.6_7)(127.9_7)$	126.6_1	128.8_9	

(a) *ortho*-Substituent in Ar. (b) *para*-Substituent in Ar. (c) Alcohol corresponding to XIIb.

The compounds examined and their ^{13}C chemical shift values are given in Tables 1-5. It should be noted that, provided the aryl groups are *cis* to each other (which can be easily recognized by the equivalence of corresponding aromatic carbon signals), only two configurations and three conformations: VIIa, chair-chair, VIIb, boat-chair and the

configurational isomer VIII, chair-boat need be considered (Scheme 2). (The boat-boat conformation of VII and the chair-chair conformation of VIII suffer from *syn*-axial aryl/aryl interactions and boat-boat conformations are, in any case, unlikely (9) for either VII or VIII.)

Scheme 2



cis-2,4-Diphenyl-3-ABN-9-one (Xa) (33,34) as well as the corresponding hydrocarbon, *cis*-2,4-diphenyl-3-ABN (IXa) (34), are known, from crystallographic data, to exist in the chair-chair form (corresponding to VIIa) in the solid state. As discussed above, the conformation in solution must therefore correspond to either VIIa or VIIb, the configuration being given by the X-ray structure. A change from VIIa to VIIb upon dissolution besides being inherently unlikely is not in accord with the chemical shift of C(7) at 22.15 ppm (*cf.* Scheme 1 above); C(7) in BCN resonates at 23.01 (35). Thus IXa and IXb [C(7) at 21.20 - the corresponding resonance in BCN-9-one comes at 21.06 ppm (36)] appear to be very largely double chair forms in solution. This is also true for the *para*-substituted compounds Xd, Xf, Xh, in view of the correspondence of their shifts with those of Xa, and of the *N*-methyl analogs IXb, Xb and Xi in which a sizeable downfield shift (9-10 ppm) relative to the corresponding N-H compounds IXa, Xa and Xd is seen only at C(2,4), where it would be expected as a result of the β-effect of the *N*-Me substituent. Further evidence for the double chair form comes from the chemical shift values for C(9) in IXa and IXb (37.26, 36.57) which are close to the value of 35.42 in BCN (35,36). The shifts at C(6,8), 26.16 and 26.59 ppm (36), are upfield of those in BCN (35) (31.98 ppm) as would be expected on the basis of the enhanced γ-gauche effect produced by a first-row heteroatom (38). The chair-chair conformation assigned to 3-ABN's on the basis of these shifts is in accordance with assignments by other methods (15,18-20). The *cis-cis* (and thus presumably diequatorial) orientation of the aryl groups follows from the equivalence of their signals and is in accordance with proton nmr spectroscopic evidence (18).

The 3-ABN's with *ortho*-substituted aryl groups at the C(2,4) positions probably also exist in chair-chair conformations (VIIa) contrary to previous reports (15,16). This conclusion is based on the close similarity (Table 2) of the C(9), C(7) and C(6,8) shifts in the unsubstituted (Xa), *para*-substituted (Xd,f,h) and corresponding *ortho*-substituted (Xc,e) compounds. C(2,4) is about 3 ppm upfield in the *ortho*-CH_3 compound Xc relative to the *para* isomer Xd; the corresponding shift in the methoxy compounds (Xe,f) is 6.5 ppm. However, such upfield shifts (corresponding to γ-effects) are normal: C_α in *o*-diethylbenzene (25.3 ppm) is almost 4 ppm upfield from that in ethylbenzene or *m*-diethylbenzene (29.1) (39). Corresponding data for *o- vs.* p-ethylanisole are not available, but the upfield shift of the ring methyl carbon in *o*-methylanisole relative to the *para* isomer (4.2 ppm) is much larger than the corresponding shift in *o- vs. p*-xylene (1.7 ppm) (39). The effect of *N*-methylation in Xk (relative to Xe) is similar to that in the phenyl analog Xb (relative to Xa). (We shall later discuss the apparently anamalous spectrum of the *o*-chloro compound Xj.) The only point of concern is the sizeable shift (3.4-3.9 ppm) of C(1,5) in the *ortho*-substituted compounds Xc and Xe relative to the *para* isomers Xd and Xf (Table 2); no corresponding ϵeffects are found in simple model compounds [C_β in *o*-diethylbenzene is 0.5 ppm upfield from the corresponding carbon in ethylbenzene (39)]. We are inclined, in view of the constancy or appropriateness of all other shifts, to ascribe this anomaly to a deformation of the (strained) aryl compounds with ortho substituents rather than to a change to the chair-boat form. In this connection it is comforting that the epimeric alcohols XIIIe and XIIIf (Table 3), which are derived from Xc by reduction, differ from each other in chemical shift much as any other corresponding epimeric pair (*vide infra*). If the nitrogen-containing ring were in the boat form, one would expect profound differences between these two epimers, since one of them would have the hydroxyl group in close proximity (hydrogen-bonded?) to the nitrogen and the other would not.

Introduction of a *t*-butyl group at C(7) in 3-ABN (IXc,d) and 3-ABN-9-one (Xg) does not materially alter the chemical shift values for the C(1,5), C(2,4), C(6,8) and C(9) carbons, suggesting a chair-chair conformation with the bulky *t*-butyl group in the equatorial orientation. It is known (40) that an equatorial *t*-butyl group has little effect on the chemical shifts of C(2,6) (cyclohexane numbering), C(3) or C(4), the lack of change at C(2,6) being due to compensating downfield shifting β- and upfield shifting γ-effects. The α-effect at C(7) - *ca.* 19 ppm - is also comparable to that at C(1) in *t*-butylcyclohexane (21.2 ppm) (40).

2,4-Diphenyl-7-T-3-ABN-9-one (XIa, Table 4) and the analogous *p*-chlorophenyl compound XIb do not seem to be in the chair-chair conformation. This may be deduced from a comparison of XIa with Xa and an analogous comparison of 4-thiacyclohexanone with cyclohexanone (38) as summarized in Table 6. While all of the differences between XIa and Xa, compared to corresponding differences in model compounds where possible, are disturbingly large, that for the α-position, next to sulfur [C(2,4) in the 7-T-3-ABN-9-one], is outside of all reasonable limits for a pure chair-chair conformation and suggests a chair-boat

[*cf.* (37)] in which the nitrogen-containing ring is in the boat form (configuration and conformation VIII, Scheme 2). This change should lead to an upfield shift of all carbons in the nitrogen-containing ring (*cf.* VIb *vs.* VIa in Scheme 1) and this is seen at C(1,5), C(9) and probably also C(2,4) (Table 6). The shift at C(6,8) (or C_α) can, unfortunately, not be predicted, but a major change at this position is expected as one goes from chair-chair to chair-boat.

Table 6
Difference in Chemical Shifts Between 4-Thiacyclohexanone (or XIa) and Cyclohexanone (or Xa)

Carbon (a)	α(6,8)	β(1,5)	γ(9)	C(2,4)	*ipso*
Monocycles (b)	+2.90	+2.10	−3.30	n.a. (c)	n.a. (c)
XIa *vs.* Xa (d)	+8.36	+1.01	−4.42	−1.26	+3.31
Δ (e)	+5.46	−1.09	−1.12	(−1.86) (f)	

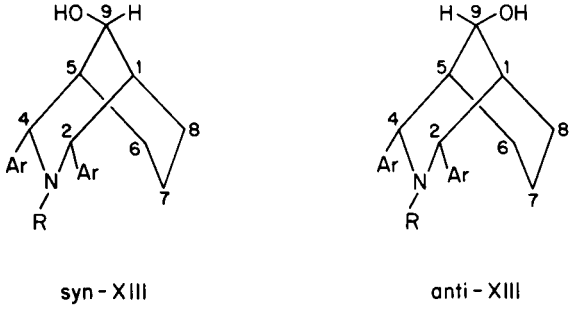
(a) α, β and γ are positions relative to sulfur. (b) Shift in 4-thiacyclohexanone minus shift in cyclohexanone. (c) Not applicable. (d) Shift in thia compound XIa minus shift in reference compound X_a. (e) Shift difference in bicyclo compounds minus shift difference in model cyclohexanones. (f) Assuming that the insertion of sulfur at C(7) should not affect the shift of C(2,4).

All this suggests conformation VIII for the ring framework of XIa, but while the nmr data convincingly exclude a chair-chair conformation, one might contemplate the alternative of an equilibrium involving a chair-boat interconverstion of the sulfur-containing ring, with the nitrogen-containing one remaining as a chair (Scheme 2, VIIa ⇌ VIIb). However, as we shall discuss in connection with the conformation of alcohol XIVa below, such an explanation is not tenable.

Several 2,4-diaryl-3-azabicyclo[4.3.1]decane derivatives (XII) were also examined (Table 5). However, because of the lack of suitable models and the greater conformational mobility of the seven-membered ring compared to the six-membered one, definitive conclusions as to conformation were not reached.

We turn now to the 3-ABN-9-ols (XIII) and their acetates in Table 3. These compounds may exist as *syn* or *anti* isomers (Scheme 3). We first note that the chemical shift of C(7) is practically unaltered by the introduction of a hydroxyl group at C(9), regardless of configuration (compare Table 3 with Tables 1 and 2). This supports the assumption that all compounds exist in chair-chair conformations; for if the nitrogen containing ring existed as a boat (*cf.* VIII), one of the epimeric alcohols might engage in intramolecular hydrogen bonding and the other would not, which would probably lead to changes in shift of C(9). In fact, however, the shift is remarkably invariant (Table 3). Again if the carbocyclic ring existed in a chair-boat equilibrium (*cf.* VII), such equilibrium should be greatly affected by the position of the 9-hydroxyl group and this, in turn, should affect the shift of C(7). Once again (Table 3), the shift of C(7) is quite invariant throughout the series.

Scheme 3



syn - XIII anti - XIII

Assuming a chair-chair conformation, the configuration at C(9) can be readily inferred from the shifts of C(2,4) and C(6,8). It is evident from Scheme 3 that in the *anti* configuration the hydroxyl group is axial to the ring containing C(6,8) which should thus be shifted upfield by the usual γ_a effect (41). In contrast, in the *syn* configuration the hydroxyl is axial in the nitrogen-containing ring and the upfield γ_a shift should affect C(2,4). Indeed, contemplation of epimeric pairs (XIIIa/b, XIIIc/d, XIIIh/i, XIIIm/n) shows (Table 3) that C(6,8) is always around 26.5 ppm in one epimer and 19.5 in the other; the former may thus be assigned the *syn* configuration and the latter the *anti*. Correspondingly, C(2,4) are upfield in the first member of each pair and downfield in the second. [The actual shifts of C(2,4) also depend on whether or not there is a (downfield shifting) *N*-methyl group and whether or not there is an (upfield shifting) *ortho* substituent in the aromatic ring.] In this way we may assign the *anti* configuration not only to XIIIb,d,f,i,n, but by analogy, also to the single epimers XIIIg and XIIIj. By the same token, the *syn* configuration may be assigned not just to XIIIa,c,e,h,m but also to XIIIk,l,o,p,q. And while the configuration of the acetates XIIIw-z (Table 3) follows, of course, from that of their precursor alcohols, an independent (and consistent) assignment can be made on the basis of the C(2,4) and C(6,8) shifts: XIIIw and XIIIx are *syn* and XIIIy and XIIIz are *anti*. The internal consistency is also seen for the NH compounds XIIIa,b,f,k,o and the corresponding *N*-methylated derviatives XIIIc,d,g,l,p.

The configurations arrived at for XIIIa/b and XIIIc/d by this method are the opposite of those suggested by both Baliah and Jeyaraman (15,19,42) and (in the case of XIIIa/b) Azerbaev, Omarov and coworkers (43) on the basis of less conclusive methods [order of elution on column chromatography (42), relative rates of acetylation (19), infrared spectroscopy (15,43)]. Specifically, in the XIIIa/b series, the lower-melting isomer, previously assigned (42,43) the *exo* or *anti* configurations, is, in fact, *syn*-XIII (Scheme 3, R = H, Ar = C_6H_5) and the higher-melting isomer, previously considered (42,43) *endo* or *syn*,

is, in fact, *anti* (Scheme 3). Configurations of compounds XIIIe-g reported (15a,19) are the same as those now established; however the chair-boat conformation earlier proposed (15a) on the basis of the appearance of two stretching bands in the infrared spectra (one ascribed to intramolecular hydrogen bonding) appears to be incorrect. Possibly the sharp peak at 3570-3575 cm^{-1} previously assigned to intramolecularly bonded hydroxyl in fact corresponds to unbonded hydroxyl, with intermolecular bonding (which gives rise to a broad lower frequency peak) being partially inhibited by the bulky *ortho* substituents of the phenyl rings. In contrast, although the correct chair-chair conformation was previously assigned (15a,19) to the isomeric pair XIIIh/i, their configurations, as well as those of their *N*-methyl derivatives (15a,19) must also be reversed. The configurations here assigned on the basis of the ^{13}C nmr spectra have been independently confirmed by mass spectrometric investigations based on the intensity of M-17 peaks (44).

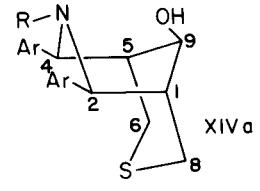
It is of interest that only the *syn* isomer (*syn*-XIII) is produced in the formation of XIIIk,l,o,q by reduction of the corresponding ketone, perhaps suggesting preferred approach by hydride from the side of the (less crowded) carbocyclic ring. Accordingly, in the cases where both epimeric alcohols are formed, the *syn* isomer is usually the preferred one.

The conversion of BCN to BCN-9-ol leads to an upfield shift of about 7.5 ppm for one of the pairs of equivalent methylenes (evidently the one *syn* to the hydroxyl) and no appreciable shift of the other (*anti*) pair (45). C(1,5) shifts downfield about 6.5 ppm, C(7) upfield by about 1.5 ppm (45). Very similar shifts are seen in the change from IXa and IXb to XIIIa and XIIIc, supporting the hypothesis that since BCN and its derivatives exist as double chairs, the same is true of 2,4-diaryl-3-ABN and its congeners.

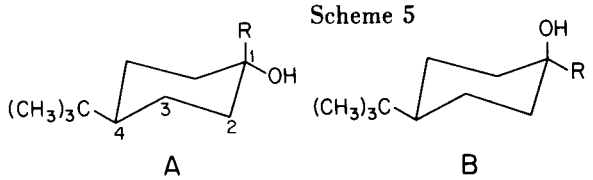
We return now to the 7-thia compounds in Table 4, especially the ketone XIa and the corresponding alcohol XIVa. We note that in going from XIa to XIVa C(2,4) shifts only 1.44 ppm upfield and this would suggest (*vide supra*) that XIVa is the *exo* alcohol. However, this would then imply a large (*ca.* 9.7 ppm) upfield shift for C(6,8). In fact, these carbons shift upfield by only 3.27 ppm which is close to the expected shift (*ca.* 2.8 ppm) in the *endo* isomer. This internal inconsistency supports our earlier hypothesis that XIa (and hence XIVa and the other thia compounds in Table 4) exist with the nitrogen-containing ring in a boat form (Scheme 4). If XIa existed in a conformation with the *sulfur*-containing ring partly or largely in the boat form (similar to VIIb, X = S, Scheme 2), one would expect a reversion to the double chair as the ketone is reduced to the alcohol [boat forms are more likely in BCN-9-ones than in corresponding compounds sp^3 hybridized at C(9) (46), just as the boat form is more accessible in cyclohexanones than in cyclohexanes (9)]. The chemical shift evidence speaks against this possibility, especially since, for steric reasons, one would expect the alcohol in a conformation corresponding to VIIb to be axial to the chair (to avoid serious transannular interaction with the sulfur atom in the boat), in which case C(2,4) should be shifted strongly upfield (which they are not). We also note that in the acetylation of XIIIc and XIIIg (chair-chair conformations), respectively, to XIIIw and XIIIy there is little change of shift at C(2,4), C(6,8) and C(7) and there is (as expected upon acetylation of an alcohol) a small downfield (β) shift at C(9) and a somewhat larger upfield (γ) shift at C(1,5). In contrast, the shifts in going from alcohol XIVb to acetate XIVc are substantial at C(2,4) and C(6,8) and the shift at C(1,5) is downfield rather than upfield. This anomaly once again speaks against the 7-thia compounds being in chair-chair conformations. Indeed, since our nmr studies were completed, the boat-chair conformation XIVa (Scheme 4) has been confirmed by X-ray crystallography (47) and similar results have been reported in the 2,4,6,8-tetraaryl analogs (48).

We now turn to the 9-hydroxy-9-alkyl-2,4-diaryl-ABN's, XIIIr-v, obtained by the action of Grignard reagents on the corresponding ketones. The presence of geminal substituents at C(9) should favor the chair-chair configuration over chair-boat or boat-chair because of unfavorable transannular interactions in the latter; this is in agreement with the invariance of the C(7) relative to that of other compounds and the predicted trends at C(1,5) and C(9) (slight downfield shift) and C(6,8) (*vide infra*). The configuration of alcohols XIIIr-v can be assigned on much the same grounds as those of the secondary 9-hyroxy-9-H analogs (*vide supra*) except that, instead of an absolute γ_a effect of the hydroxyl group on C(2,4) or C(6,8), respectively, one must now consider a differential effect of OH *vs.* Ph or Me. This can readily be done on the basis of known ^{13}C nmr data for conformationally locked 1-methyl- and 1-phenylcyclohexanols (49) shown in Scheme 5 which clearly indicate that the γ_a effect of hydroxyl is larger than that of methyl or phenyl. Given that fact one can assign configuration to the epimeric pair XIIIr/XIIIs. In XIIIr C(6,8) (20.49 ppm) is relatively upfield and C(2,4) (60.72 ppm) relatively downfield of the corresponding signals in XIIIs (23.64, 58.73). It may thus be concluded that the OH group

Scheme 4



Scheme 5

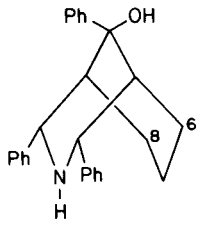


Scheme 5

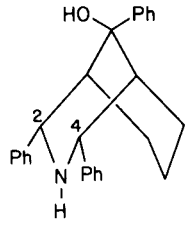
compound/carbon	1	2	3	4
A,R = CH_3	70.9_2	40.8_9	24.9_9	47.7_9
A,R = C_6H_5	73.2_2	38.7_4	24.9_2	47.6_8
B,R = CH_3	68.8_3	39.3_9	22.7_1	47.7_7
B,R = C_6H_5	72.7_3	39.3_9	22.8_9	47.5_3

is on the side of the carbocyclic ring in XIIIr, but on the side of the nitrogen-containing ring in XIIIs (Scheme 6). Moreover, from the constancy of the C(6,8) signals, it may be inferred that XIIIt, XIIIu and XIIIv correspond in configuration to XIIIs, *i.e.* have the *syn* hydroxyl group. [Once again, this corresponds to an approach of the Grignard re-

Scheme 6



XIIIr



XIIIs

agent from the less encumbered side of the cyclohexane (rather than diarylpiperidine) ring.] The position of C(2,4) in XIIIu and XIIIv also corresponds to that in XIIIs (and is different from that in XIIIr). In the case of XIIIt, C(2,4) are, of course, quite downfield because of the β-effect of the *N*-methyl group observed in other cases in Table 3. However, quite apart from the fact that the configuration of XIIIt necessarily corresponds to that of XIIIs from which it is derived by *N*-methylation, the downfield shift of C(2,4) (XIIIs → t) of +9.27 ppm closely corresponds to that in other NH/NMe pairs (XIIIa/c, +8.96 ppm, XIIIb/d, +9.63 ppm).

We finally note that one of the aryl signals - probably that due to the *ortho* carbons - in most of the *N*-methyl compounds studied (IXb,d; Xb, XIIIc,d,j,t,w,z) is substantially broadened, presumably due to restricted rotation of the phenyl ring. The stable conformation of this ring is probably (50) one in which it is parallel to the C(1)-C(6) bond and restricted rotation leads to unequal environment for the two *ortho* carbon nuclei. Upon heating to 55° the signal sharpens in the case of IXb (the other compounds were not studied). Not surprisingly the broadening does not occur with the NH compounds, presumably because phenyl rotation is fast on the nmr time scale. Interestingly, *no* broadening is seen either in the *ortho*-substituted compounds Xk and XIIIg,l,p,x and y. We ascribe this to the fact that these compounds are probably anancomeric, *i.e.* strongly biassed toward the conformation in which the *ortho* substituent points in the direction opposite the methylene carbons 6 and 8 and therefore no significant site exchange occurs under conditions of either fast or slow rotation of the phenyl ring. A somewhat anomalous spectrum is displayed by the *N*-methyl-*cis*-2,4-di(*o*-chlorophenyl)-ABN-9-one Xj. Both C(1,5) and N-CH_3 are about 6-7 ppm downfield from their normal positions (as in Xb). We believe that the dipolar replusion between the *ortho*-chloro dipoles and the C(9) carbonyl dipole leads to a substantial tilt of the plane of the phenyl rings from their otherwise preferred positions. This, in turn, causes downfield-shifting steric compression effects by the δ substituents: on N-Me by the unsubstituted *ortho* carbons of the aryl rings and on C(1,5) by the *ortho*-chloro substituents.

Conclusion.

The ^{13}C nmr spectral evidence is persuasive in leading to a chair-chair assignment of the non-aromatic rings in all *cis*-2,4-diaryl-9-ABN's here studied regardless of whether the substituents at C(9) are H, H; =O; H, OH; R, OH or H, OAc and regardless of whether the aryl groups are unsubstituted or bearing *ortho* or *para* substituents. The configuration of the 9-ols (secondary or tertiary alcohols) as *syn* or *anti* can be readily inferred from the ^{13}C spectra. Only in *cis*-2,4-diaryl-7-T-3-ABN's does a chair-boat conformation predominate corresponding to the configuration in which the nitrogen-containing ring is a boat an the sulfur-containing one is a chair.

EXPERIMENTAL

^{13}C NMR Spectroscopy.

The ^{13}C nmr spectra (25.16 MHz) were recorded by means of a Varian XL-100 pulsed Fourier transform spectrometer in FT mode in 5- or 10-mm o.d. tubes in deuteriochloroform (solvent and lock substance) containing TMS; sweep width 5120 Hz or 6120 Hz, 30° pulse angle, 0.8 s pulse interval and 1000-4000 transients per spectrum (depending on concentration). Fourier Transforms were based on 8K data points. The spectrometer was controlled by a 620/f computer. Shift assignments (except in the case of ortho and meta carbons in the aromatic rings) were, in almost all cases, obvious from signal intensities and chemical shifts, and confirmed in some cases, from SFORD spectra.

Syntheses.

The syntheses of all the compounds with the exception of IXb, Xc, XIIIt and XV have been reported previously (15b, 19,44,51,52).

Compounds IXa, Xa, Xd-f and Xh were obtained according to the procedure of Baliah and Jeyaraman (51) and IXc,d and Xg by the procedure of Jeyaraman, Chockalingam and Rajendran (53). The procedure for the synthesis of compounds Xb,i-k XIIIa-j, XIIIo-q and XIVa,b was similar to that reported (42) and the alcohols XIIIk-n were also obtained by the same procedure (15b). The tertiary alcohols XIIIr,s and XIIIu,v were obtained by Grignard addition to the corresponding ketones (15b). The esters XIIIw-z and XIVc were obtained as reported (54). Compounds XIa,b were prepared by the usual condensation reaction (9). The condensation of aldehydes and ammonium acetate with cycloheptanone gave XIIa-d (52).

3-Methyl-2,4-diphenyl-3-ABN (IXb).

A pure sample of 2,4-diphenyl-3-ABN on methylation (42) with

dimethyl sulfate yielded IXb which was recrystallized from ethanol, mp 122-123°, yield 85-90%.

Anal. Calcd. for $C_{21}H_{25}N$: C, 86.60; H, 8.59. Found: C, 86.45; H, 8.72.

2,4-Bis(*o*-tolyl)-3-ABN-9-one (Xc).

Starting with *o*-tolualdehyde, cyclohexanone and ammonium acetate this ABN was obtained following the general procedure described earlier (51). The ketone was recrystallized from benzene petroleum ether, mp 217-218°, yield 35-40%.

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.76; H, 7.84. Found: C, 82.65; H, 7.91.

3-Methyl-2,4,9-triphenyl-3-ABN-9-ol (XIIIt).

N-Methylation of 2,4,9-triphenyl-3-ABN-*trans*-9-ol (XIIIs) employing dimethyl sulfate gave XIIIt. On recrystallization from benzene-petroleum ether it melted at 174-175°, yield 75-80%.

Anal. Calcd. for $C_{27}H_{29}NO$: C, 84.60; H, 7.57. Found: C, 84.35; H, 7.70.

Acknowledgements.

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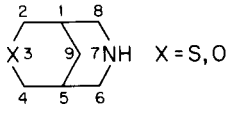

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