cis- & trans-6-Amino-6, 7, 8, 9-tetrahydro-5 H-benzocyclohepten-5-ols, 10-Amino-10, 11-dihydro-5H-dibenzo(a, d) cyclohepten-11-ols and 4-Amino-2, 3, 4, 5-tetrahydro-1-benzoxepin-5-ols

J. M. KHANNA, BANSI LAL, V. K. TANDON and NITYA ANAND*

Central Drug Research Institute, Lucknow

With a view to increasing our understanding of the conformation of catecholamines representing an 'ideal' fit of the molecules at the adrenergic receptor site, cis- and trans-2-hydroxy-, 3-hydroxy and 2, 3-dihydroxy-6-amino-(and isopropylamino)-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols and some related compounds, which incorporate a phenyl-ethanolamine residue, a common denominator of many adrenergic compounds, in a rigid framework, have been synthesised and their biological activity studied. Some significant differences between the properties of 6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols and the corresponding aminotetralols, indanols and acyclic compounds are : (i) very facile acid catalysed epimerisation of both cis and trans-isomers (3N HCl for 30 at 100°), and (ii) N←O-acetyl migration taking place in both cis and trans-isomers with retention of configuration. Only in the case of 6, 7-trans-7-phenyl-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols and 4-amino-2, 3, 4, 5-tetrahydro-1-benzoxepin-5-ols it has been found that only the trans-isomer undergoes epimerisation and gradually an increasing proportion of the cis-isomer accumulates in the reaction mixture. Stereochemical assignments and proposals for probable conformations are based on nmr studies. A twist chair conformation has been proposed for cis- and trans-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols, while for 6, 7-trans-5, 6-cis- and trans-7-phenyl-6, 7, 8, 9-tetrahydro-5H-benzocycloheptenols the nmr data can be best fitted for boat conformations. A characteristic feature of the nmr spectra of these compounds was the marked downfield shift of H-4, which is peri to the 5-OH group, in one of the isomers ; the OH group in this isomer has been assigned equatorial geometry. In a further study of the nature of this deshielding effect 5, 7-cis- and trans-7-phenyl-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols and their corresponding O-methyl and O-acetyl derivatives have been synthesised and their nmr studied ; it has been found that the extent of deshielding is related to the availability of the lone pair of electrons on the oxygen. The formation of hydrogen bond between H-4 as donor and OR (R=H, Me, Ac) as acceptor may be involved. Both cis- and trans-2, 3-dihydroxy-6-amino-6, 7, 8, 9-tetrahydro-benzocycloheptenols show typical α-sympathomimetic activity. These findings have been discussed in terms of the probable structural profile of α-adrenergic receptor.

CATECHOLAMINES and related adrenergic amines can take a number of 'permissible' conformations at the receptor site. This stereochemical aspect of adrenergic amines has received considerable attention. In an understanding of the adrenergic receptor it is important to know the conformation of the agonist for the 'ideal' fit at the receptor site. Rigid molecules with severely limited permissible conformations, and having the biological activity of the prototype can prove helpful in this analysis. Compounds which have a phene-thanolamine residue, a common denominator of many adrenergic amines, incorporated in a rigid frame-work could thus serve as useful probes for delineating the structural dimensions of the adrenergic receptor, and have been a subject of study in this laboratory. 6-Amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols is one such structure. Synthesis of its isomers as also of its 2- and 3-hydroxy, and 2, 3-dihydroxy analogs and some related compounds, study of their

conformations and biological activity and delineation of the structural profile of the adrenergic receptors based on these findings is presented in this paper.

I. 6-Amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols

The synthesis and stereochemistry of cis- and trans-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols[1,2] is outlined in Chart I. Most of the ketones 1 required as starting materials were either known compounds or were prepared by known methods.[3-7] 2-Hydroxy and 2, 3-dihydroxy-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ones (1g and 1m) were prepared by demethylation of the corresponding methoxy ketones using Py.HCl or AlCl₃-PhH, and were converted to the corresponding benzyl ethers by treating the phenols with PhCH₂Cl-K₂CO₃ in Me₂ CO. 2, 3-Diacetoxy-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (1k) was prepared by heating 1m

with Ac$_2$O. Oximino ketones 2 were obtained by treating the ketones 1 with n-BuONO in presence of dry HCl, NaOEt or KOEt. Oximino ketones 2 on catalytic hydrogenation or LiAlH$_4$ reduction gave cis-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols (4), whereas

the substituents at positions 2 and 3, on 6-amino group and of the nature of the metal hydride on the stereoselectivity of the reduction are noteworthy. The difference between the stereoselectivity of NaBH$_4$ and LiAlH$_4$ is very likely related to the larger "effective" bulk of NaBH$_4$ due to solvation. It is likely
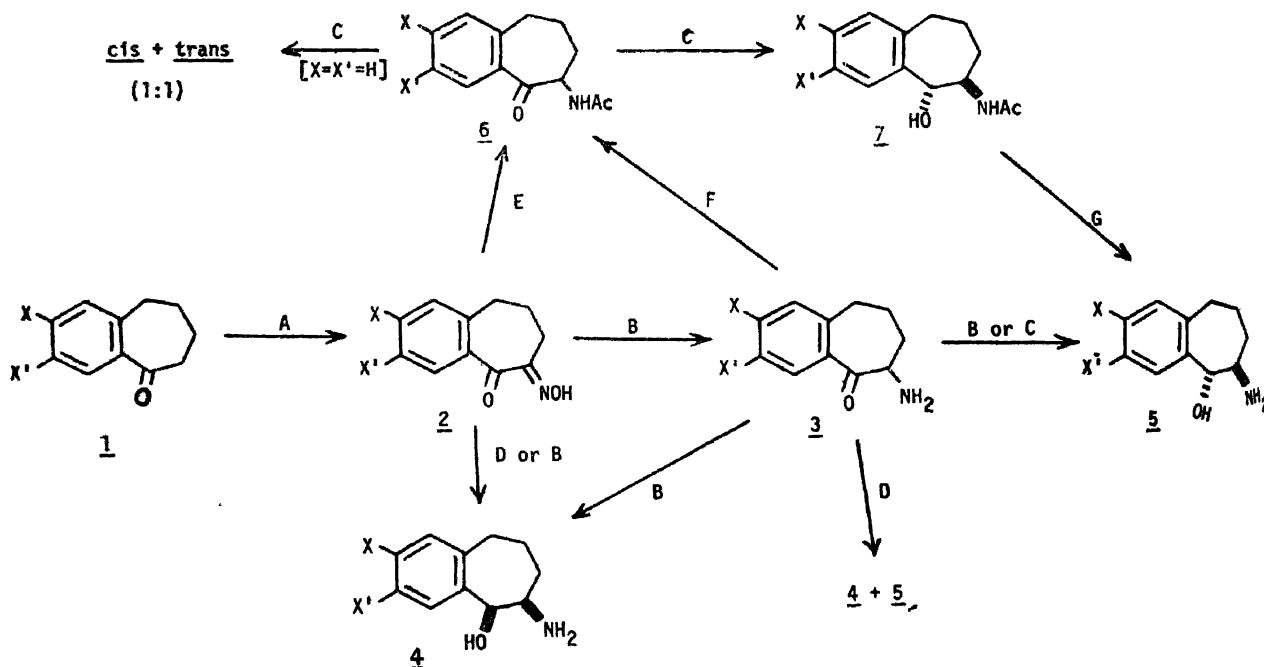
A. n-BuONO, KOEt or HCl; B. 10% Pd/C, MeOH, HCl; C. NaBH$_4$; D. LiAlH$_4$; E. 10% Pd/C,

Ac$_2$O-AcOH; F. Ac$_2$O-NaOAc; G. 3N NaOH.

(a) X=X'=H; (b) X=X'=OMe; (c) X=X'=Me; (d) X=H, X'=OCH$_2$Ph; (e) X=OCH$_2$Ph, X'=H;

(f) X=H, X'=OH; (g) X=OH, X'=H; (h) XX'=-(CH$_2$)$_4$-; (i) X=H, X'=OMe; (j) X=OMe, X'=H;

(k) X=X'=OAc; (l) X=X'=OCH$_2$Ph; (m) X=X'=OH.

CHART I

catalytic hydrogenation in presence of Ac$_2$O-AcOH stopped at the stage of 6-acetamido-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ones (6) also obtained when 3 was treated with Ac$_2$O -NaOAc. 2, 3-Disubstituted 6-acetamido-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ones (6) on NaBH$_4$ reduction gave trans-6-acetamido-benzocycloheptenols (7) as a major product, whereas reduction of 6-acetamido-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (6a) with NaBH$_4$ gave a 1:1 mixture of cis- and trans-isomers 8a and 7a.

6-Amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ones (3) on reduction with NaBH$_4$ gave the corresponding trans-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols (5) as the major product. In contrast, LiAlH$_4$ reduction of 3 gave a 1:1 mixture of cis- and trans-compounds. These subtle effects of

that the N in the amino ketone 3a would be able to complex better with the metal hydride than the acetamido ketone 6a, and this may be the reason for the greater stereoselectivity of reduction of the aminoketone as compared to that of the acetamido ketone. The effect of the substituents at position 2 and 3 is obviously due to their electron donation, which would increase electron density at position 5.

Catalytic hydrogenation of 6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (3a), in most of the experiments, gave only the trans compound, but occasionally only the cis compound was formed. The exact conditions under which this happens could not be established.

cis- or trans-6-Amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (4a or 5a) on treatment with

Ac₂O-MeOH or *p*-nitrophenylacetate in EtOAc gave the corresponding *cis*- or *trans*-6-acetamido-benzocycloheptenols (*8a* or *7a*), while treatment with Ac₂O alone gave the corresponding *cis*- or *trans*-N, O-diacetyl compounds.

duration of heating, and after about 4 hr heating an almost equal proportion of the two isomers, as determined from NMR, was formed. In experiments where HCl heating was carried out for 24 hr in addition to *cis*- and *trans*-aminobenzocycloheptenols, a
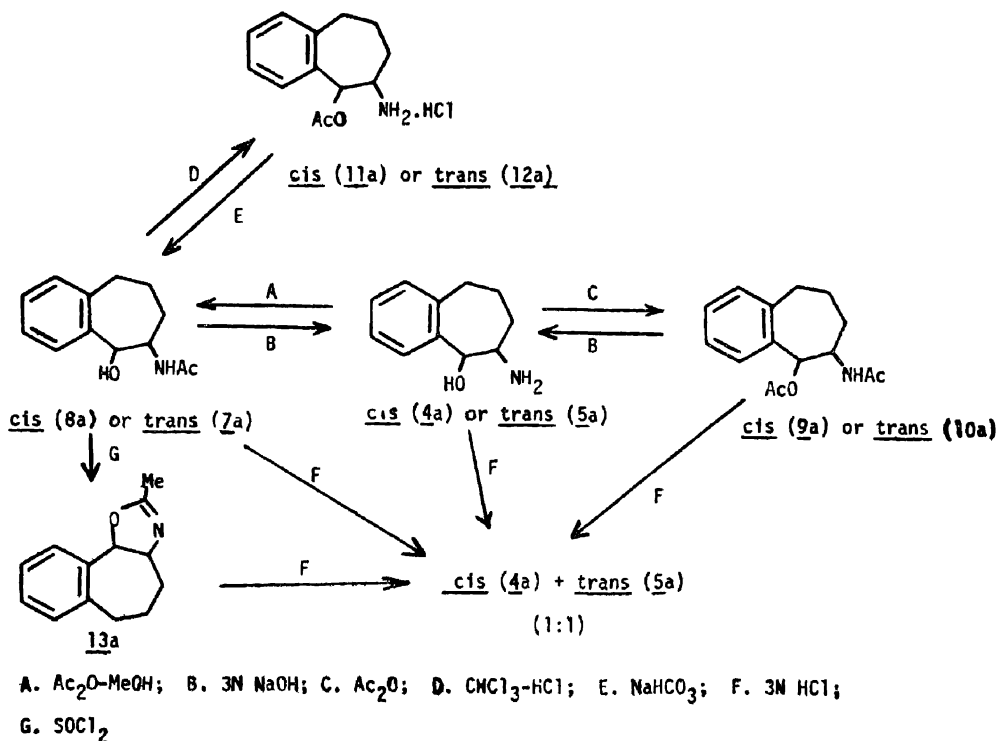

CHART II

Vicinal N-acylaminoalkanols undergo an acid catalysed N→O acyl migration[8-10], without inversion if the cyclic intermediate formation is sterically favoured and with inversion if the cyclic intermediate formation is sterically not favoured. In the present case, it was found that both the *cis*- and *trans*- N-acetyl compounds *7a* and *8a* when treated with CHCl₃-HCl gave the corresponding O-acetyl compounds *11a* and *12a* respectively, without inversion (N→O acetyl migration was less facile in the case of the *trans* compound and a small quantity of the *trans*-aminoheptenol *5a* was also formed) ; treatment of the O-acetyl compounds *11a* and *12a* with NaHCO₃ regenerated the N-acetyl compound without inversion (Chart II). When either *cis*- or *trans*-6-acetamido-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (*7a* or *8a*) was treated with 3N HCl, a mixture of *cis* and *trans* compounds *4a* and *5a* was formed. This epimerization also took place when *cis*- and *trans*-N, O-diacetyl compounds or *cis*- and *trans*-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol were treated with 3N HCl in a similar manner. The extent of epimerization was determined by the

significant quantity of *β* -benzosuberone was also formed. This epimerisation very likely involves elimination of the 5-OH group by protonation leading to the creation of a carbonium ion, which can now be attacked by H₂O to form both *cis*- and *trans*-aminobenzocycloheptenols (Chart III). If in the carbonium ion, a proton from the 6-position gets eliminated 6-amino-8, 9-dihydro-7H-benzocyclo-heptadiene would be formed, which being an enamine would undergo facile hydrolysis to form *β* -benzosuberone. This mechanism is supported by the fact that when epimerisation was carried out by HCl in H₂¹⁸O, the aminobenzocycloheptenols thus obtained were found to contain ¹⁸O (determined by mass spectrum). *cis*-4, 5-benzocyclohepteno-oxazolium chloride *13a*), obtained by treatment of the *cis*-6-acetamido-6, 7, 8, 9-tetrahydro-5H-benzocyclo-hepten-5-ol (*8a*) with SOCl₂, on hydrolysis with 3N HCl also have a mixture of the *cis*- and *trans*-compounds (*4a* and *5a*).

This N⇌O acetyl migration without inversion with CHCl₃-HCl, and such a facile epimerisation by HCl
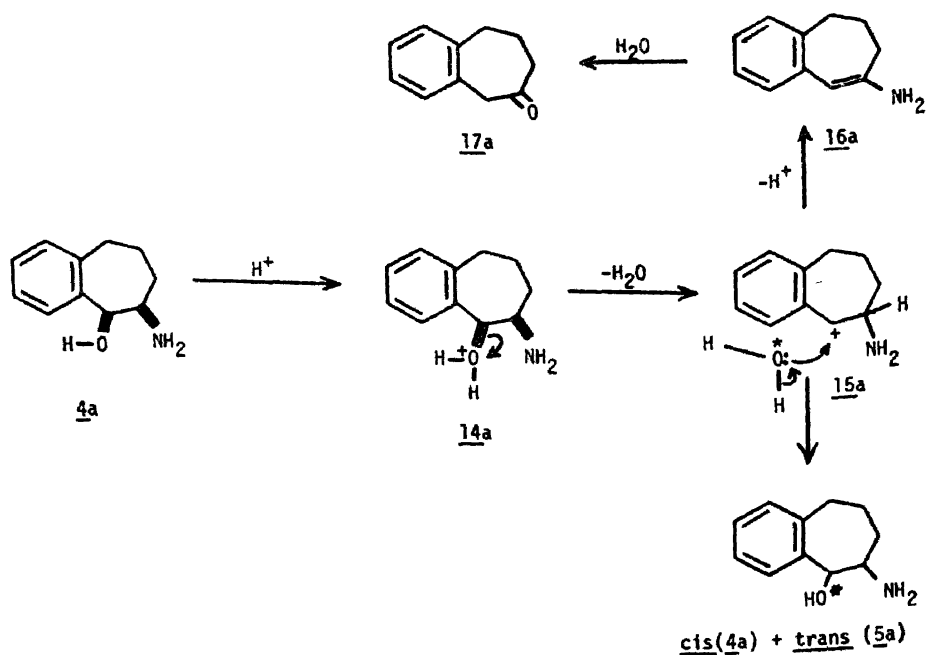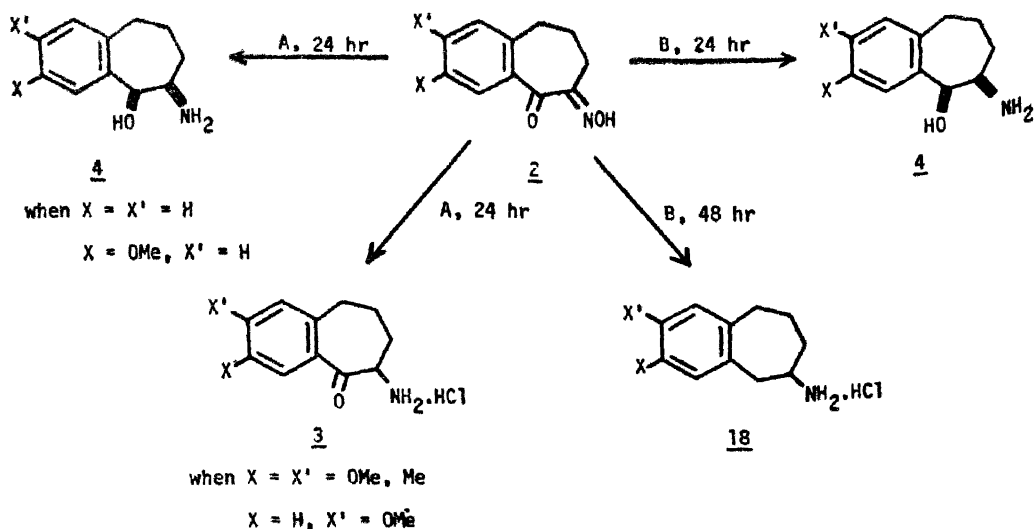
CHART III

treatment of aminobenzocycloheptenols *4* and *5* is in sharp contrast to the behaviour of the corresponding aminotetralols[10], aminoindalols[11] and acyclic compounds.[12] Similar behaviour has also been noticed with *cis*- and *trans*-10-amino-10, 11-dihydro-5H-dibenzo (a, d) cyclohepten 11-ols[13] (Chart IX).

cis- or *trans*-5-Acetamido or O, N-diacetyl

compounds on hydrolysis with $3N$ NaOH regenerated the original isomers.

The catalytic reduction of oximino ketones *2* was found to depend on the activity of the catalyst and also the nature of the substituents in the benzene ring (Chart IV). The catalytic reduction of 2-methoxy (*2j*), 2, 3-dimethyl (*2c*) and 2, 3-dimethoxy oximino

A. 10% Pd/C (K&K Lab. Inc.), MeOH, HCl; B. 50% wet 10% Pd/C (Engelhardt Co., New Jersey), MeOH, HCl.

CHART IV

ketones · *2b* in MeOH-HCl using dry 10% Pd/C stopped at the stage of the amino ketone *3*, while 3-methoxy *(2i)* and the unsubstituted oximino ketone *(2a)* gave the corresponding amino heptenols *4* under the same conditions. The same reduction using 50% wet 10% Pd/C gave the *cis*-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols *(4)* in every case and on prolonging the time of hydrogenation extensive hydrogenolysis took place and only the corresponding 6-amino-6, 7, 8, 9-tetrahydro-5H-benzocycloheptene *(18)* was obtained. The rate of hydrogenation of 2-methoxy oximino ketone *2j* was faster than that of the corresponding unsubstituted or the 3-methoxy oximino ketone *(2i)*.

Stereochemical assignments

Cycloheptenes can exist in boat, chair or twist chair conformation. The dihedral angles (ϕ) for H-5, H-6 and H-7 as measured by an examination of the Dreiding models are given in Table I.

The nmr spectrum of *4a* and *5a* is given in Fig. I. The doublet at ꝺ 5.2 (J=1 Hz) in isomer *4a* is assigned

TABLE I—DIHEDRAL ANGLES (ϕ) BETWEEN H-5, H-6 AND H-7 OF *cis*- AND *trans*-6-AMINO 6, 7, 8, 9-TETRAHYDRO-5H-BENZO-CYCLOHEPTEN-5-OL

	Dihedral angle (ϕ) cis	J, Hz	Dihedral angle (ϕ) trans	J, Hz
Boat	5a,6a = 10°	8.0	5e,6a = 110°	1.0
	6a,7a = 175°	9.0	6a,7a = 175°	9.0
	6a,7e = 90°	0.0	6a,7e = 90°	0.0
Chair	5e,6a = 90°	0.0	5a,6a = 150°	8.5
	6a,7a = 175°	9.0	6a,7a = 175°	9.0
	6a,7e = 55°	3.0	6a,7e = 55°	3.0
Twist chair	5e,6a = 100°	1.0	5a,6a = 170°	9.0
	6a,7a = 140°	6.0	6a,7a = 140°	6.0
	6a,7e = 20°	7.0	6a,7e = 20°	7.0

FIG. I

Trans isomer

Cis isomer

8.0 7.0 PPM (ꝺ) 5.0 4.0 30
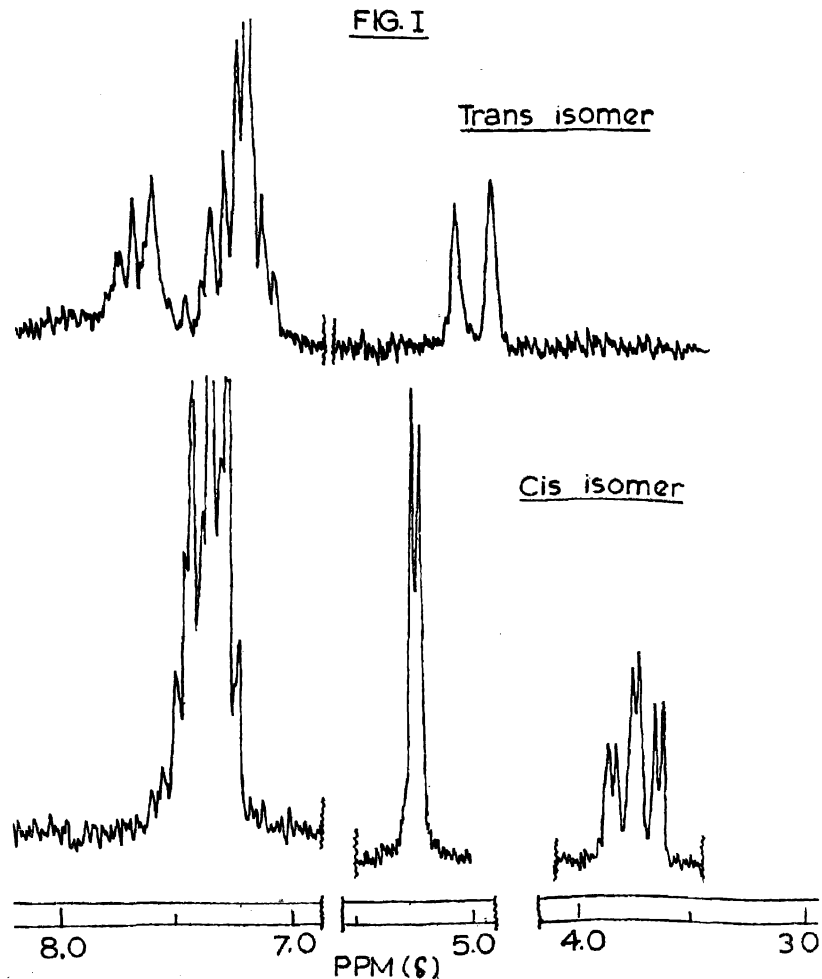
to H-5. This order of coupling could arise with cycloheptene ring in a boat conformation with 5, 6-*trans* stereochemistry (H-5e and H-6a) or in a twist chair conformation with 5, 6-*cis* stereochemistry (H-5e and H-6a). The sextet for H-6 at δ 3.7 with 2 couplings of about 6.0 and 6.5 Hz respectively, and a small coupling of *ca* 1.5 Hz is strongly in favour of this isomer having a twist chair conformation, in which case the dihedral angle between H-6 and the two 7-CH₂'s would be 20° and 135° respectively, and the 3 couplings involved would thus be of the order 7.0, 7.5 and 1.0 Hz respectively. In contrast, if this isomer had a boat conformation in 5, 6-*trans* isomer the dihedral angle between H-6 and the two 7-CH₂'s, would be about 90 and 170° respectively, and the 3 couplings involved would thus be about 1.0, 1.0 and 9 Hz and the shape of the signal would be very different. This isomer has, therefore, been assigned a 5, 6-*cis* stereochemistry and the isomer *5a* with $J_{5,6}=9$ Hz, 5,6-*trans* stereochemistry. This is further supported by the fact that aromatic H-1, H-2, H-3, and H-4 in the *cis*-isomer appear as multiplet centred at δ 7.2, while in the *trans*-isomer the aromatic H-1, H-2 and H-3 appear as multiplet centred at δ 7.2 but the signal for H-4 appeared separately as a multiplet centred at δ 7.6. This marked deshielding of H-4 in the *trans*-isomer (5a) is very likely caused by the field effect of 5-OH, which would be quasi-equatorial in this isomer. This would also be consistent with the normal upfield position (δ 4.52) of the axial H-5 in the *trans*-isomer relative to the equatorial H-5 (δ 4.85) in the *cis*-isomer. In all other cases also the isomer having $J_{5,6}=1$ Hz have been assigned the *cis* and the isomer with $J_{5,6}=8$ Hz a *trans* configuration. The conformations of 6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol are depicted in Fig. II.

The IR spectra of the two isomers did not show any marked difference in the OH stretching frequency, but there were significant differences in the finger print region. Dilution ir spectra showed that the hydrogen bonding was mainly intramolecular. There were not much difference in the pKa values of the two isomers either (*cis* isomer 8.83 ; *trans* isomer 8.95). In order to study the degree of hydrogen bonding in the two isomers, nmr at different temperatures and concentrations were recorded (Table II). These findings show that under the identical temperatures and concentrations, 5-OH group in *trans* isomer appeared downfield as compared to *cis* isomer. The known fact that less bonded OH groups appear at higher magnetic field than strongly bonded OH groups, would suggest that the degree of hydrogen

BOAT

TWIST CHAIR
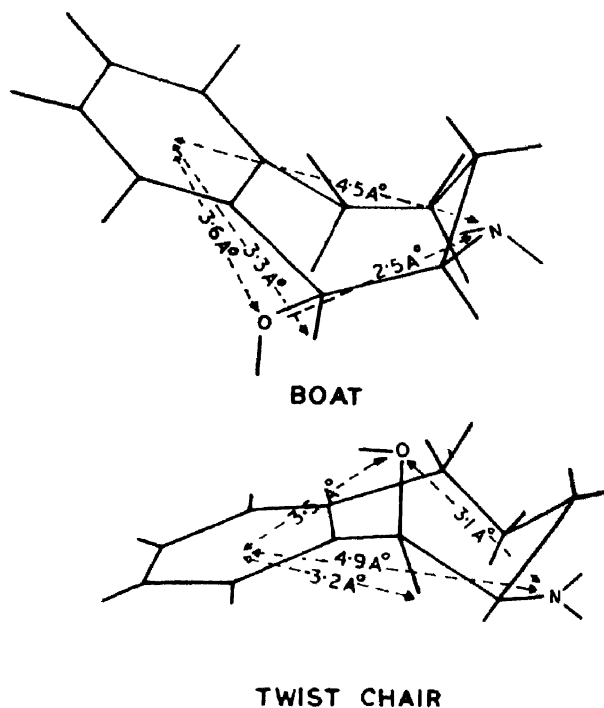
CONFORMATIONS OF 6-AMINO-6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTEN-5-OLS

(FIG. II)

bonding was more in the *trans* isomer than in the *cis* isomer.

TABLE II—HYDROGEN BONDING IN 6-AMINO-6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTENOLS*

Compound	Concentration (%) (CDCl₃)	Temperature, °C	Chemical shift (δ)
trans-Isomer	20	55	2.45
	20	45	2.50
	20	36.5	2.60
	10	36.5	2.50
	5	36.5	2.35
	2.5	36.5	2.25
	1.25	36.5	2.10
cis-Isomer	20	55	1.90
	20	45	1.95
	20	36.5	2.05
	10	36.5	1.95
	5	36.5	1.80
	2.5	36.5	1.75
	1.25	36.5	1.65

In order to understand better the nature of this deshielding of the aromatic proton peri to the 5-hydroxy radical (H-4), the nmr spectra of 5, 7-*trans*- and 5, 7-*cis*- 5-hydroxy-, 5-methoxy- and 5-acetoxy-7-phenyl-6, 7, 8, 9-tetrahydro-5H-benzocycloheptene were studied.[14] These compounds were prepared starting from 7-phenyl-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one which on $NaBH_4$ reduction gave a mixture of 5, 7-*cis*- and 5, 7-*trans*-7-phenyl-6, 7, 8, 9-tetrahydro- 5H-benzocyclohepten-5-ol which were separated by fractional crystallisation. These on treatment with MeI, NaH in DMF and Ac_2O/Py gave the corresponding 5-methoxy- and 5-acetoxy-derivatives respectively. The salient features of the nmr of these compounds are given in Table III. The isomer in which H-4 appears downfield must have 5-OH equatorial and can thus be assigned 5, 7-*cis*-configuration, and the second isomer 5, 7-*trans* geometry. The data given in the table would show that availability and the direction of the lone pair of electrons on the oxygen atom is an important

the case of equatorial 5-acetoxy compound. The probable explanation is that there is some kind of hydrogen bonding of the aromatic H-4 with the lone pair of O atom and this is maximum in hydroxy compound, because the lone pair of electrons is available to the maximum, and least in the case 5-acetoxy compound, as the carbonyl group would draw the lone pair of electrons away from the O atom ; thereby reducing the amount of hydrogen bonding. No deshielding of H-4 was observed in the case of the second isomer which would have 5-substituent in an axial orientation in which case the lone pair of electrons of O atom would be out of the plane of H-4, and, therefore, all the aromatic protons in this isomer appear in one bunch. Comparison of chemical shifts values of H-5 show that the axial protons appear downfield as compared to the corresponding equatorial protons (Table II), this is in contrast to the normally accepted chemical shift values of the equatorial and axial protons. These compounds have also been assigned twist chair conformation.

TABLE III—NMR CHARACTERISTICS OF 5, 7-*cis*- AND *trans*-5-HYDROXY, 5-METHOXY AND 5-ACETOXY-7-PHENYL-6, 7, 8, 9-TETRAHYDRO-5H-BENZOCYCLOHEPTENE
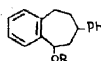

Compound		H-4		H-5		J, Hz
		Chemical shift (δ)	Nature of signal	Chemical shift (δ)	Nature of signal	
5,7-*cis*,	R=H	7.65	multiplet	4.95	quartet	10.0, 1.8
5,7-*trans*,	R=H	mixed with other aromatic protons	multiplet	4.80	quartet	6.0, 1.8
5,7-*cis*,	R=Me	7.60	multiplet	4.50	quartet	10.0, 1.8
5,7-*trans*,	R=Me	mixed with other aromatic protons	multiplet	4.30	quartet	6.0, 1.8
5,7-*cis*,	R=COCH₃	7.50	multiplet	6.20	quartet	10.0, 1.8
5,7-*trans*,	R=COCH₃	mixed with other aromatic protons	multiplet	6.10	quartet	6.0, 1.8

factor for the extent of deshielding of the aromatic H-4. The availability of lone pair of electrons is maximum in the case of 5, 7-*cis*-5-hydroxy compound, lesser in 5-methoxy compound and least in the case of 5, 6-*cis*-5-acetoxy compound. The H-4 proton in 5, 6-*cis*-5-hydroxy compound falls in the plane of equatorial OH and thereby faces directly the lone pair of O and gets deshielded, this effect was observed to a lesser extent in the case of the corresponding equatorial 5-methoxy and least in

Biological activity

The compounds were evaluated for their pharmacological activity by standard methods. The only noteworthy activity observed for these compounds was the tranquilizing activity of *cis*-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (*4a*) (LD_{50} 150 mg/kg, ip in mice). It reduced locomotor activity in mice at 15 mg/kg ip, gave protection against amphetamine toxicity (ED_{50} 73 mg/kg, po), potentiatd

barbiturate effects, showed typical effects of a tranquiliser in the EEG in rabbits, and in rats caused selective block of conditioned avoidance response. It was a weak antiemetic against apormorphine-induced emesis in dogs. It showed weak sympathomimetic activity. The corresponding *trans* isomer did not have any noteworthy activity. *4a*, however, caused signs of heat prostration in dogs when administered for a period of 3-4 weeks and does not appear to be of therapeutic use.[2] The *cis* isomer has the same configuration as ephedrine (R, S) (Fig. III). The fact that the *cis* isomer is more active than the *trans* isomer would indicate that the ephedrine configuration is necessary for the activity of these compounds. The corresponding 2, 3-dimethyl-and 2, 3-dimethoxy-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols were much less active.
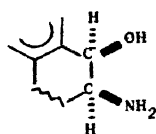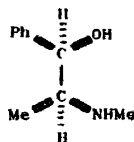
cis-6-Amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol   (-) Ephedrine

Fig. III

II. *2, 3-Dihydroxy-6-amino- and 6-isopropylamino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols*

LiAlH₄ reduction of 2, 3-dibenzyloxy-6-oximino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (*2l*) gave *cis*-2, 3-dibenzyloxy-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (*4l*), which on catalytic hydrogenation in AcOH gave *cis*-2, 3-dihydroxy-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (*4m*) (Chart V). Similarly, 2-hydroxy- and 3-hydroxy-*cis*-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols (*4g* & *f*) were prepared. *cis*-2, 3-dibenzyloxy-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (*4l*) on treatment with Ac₂O-MeOH followed by Jone's oxidation gave 2, 3-dibenzyloxy-6-acetamino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (*6l*), which was converted to *trans*-2, 3-dibenzyloxy-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (*5l*) by NaBH₄ reduction followed by base hydrolysis ; *5l* on catalytic hydrogenation in AcOH gave *trans*-2, 3-dihydroxy-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (*5m*).[15]

The size of the substituent on the amino group in catecholamines has a very marked effect on their biological activity. From pure α-type activity in

unsubstituted amino compound, there is gradual shift to α-antagonist or no α-activity to β-agonist activity as the size of the substituent becomes larger In view of the α-sympathomimetic activity shown by these dihydroxy-aminobenzocycloheptenols, it was considered of interest to synthesise the corresponding 6-isopropylamino compounds. This was carried out by condensation of *cis*- and *trans*-2, 3-dibenzyloxy-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols (*4l* & *5l*) with Me₂CO in PhH followed by NaBH₄ reduction. Catalytic hydrogenation of 6-isopropyl amino derivatives thus obtained in AcOH gave the required *cis*- and *trans*-2, 3-dihydroxy-6-isopropylamino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols (*19m* and *20m*).[15]

The nmr spectra of compounds of this group are very similar to those of 6-amino-6, 7, 8, 9-tetrahydro-5H-benzocycloheptenols described above and these compounds would, therefore, also have a twist-chair conformation.

Biological activity

Both the *cis*- and *trans*-isomer, *4m* and *5m* showed typical effects of directly acting α-sympathomimetic and there was only quantitation difference in their activity. They caused vasopressor response in normal anaesthetised cat at a dose of about 1 mg/kg iv, which was tested for 13-20 min ; the effect was dose dependent. The responses to epinephrine, norepinephrine, and tyramine were potentiated by pretreatment with them. In higher doses, they produced contraction of the nictitating membrane. The effects were much more pronounced in reserpinised cats, but greatly reduced after pretreatment with α-adrenergic blocking agents such as tolazoline hydrochloride and yohimbine.

As the *cis*- and *trans*-isomers both showed qualitatively similar effects this would point to the fact that the structural profile of the α-adrenergic receptor must be such as would accommodate both these molecules. From the nmr values these compounds appear to be present in a twist-chair conformation. The relative spatial disposition of the aromatic ring, the hydroxy and amino group would thus be the one shown in Fig. II. Hydrogen bonding studies using nmr and ir both have shown that the relative disposition of hydroxyl and amino groups is not very different in the two isomers. Both the *cis*- and *trans*-isomers having similar fit at the receptor can be due to conformational mobility of either the drug molecule, which being seven membered would have considerable

A. LAH;   B. 10% Pd/C, AcOH;   C. Me₂CO, PhH;   D. NaBH₄;   E. Ac₂O-MeOH;   F. CrO₃-Me₂CO
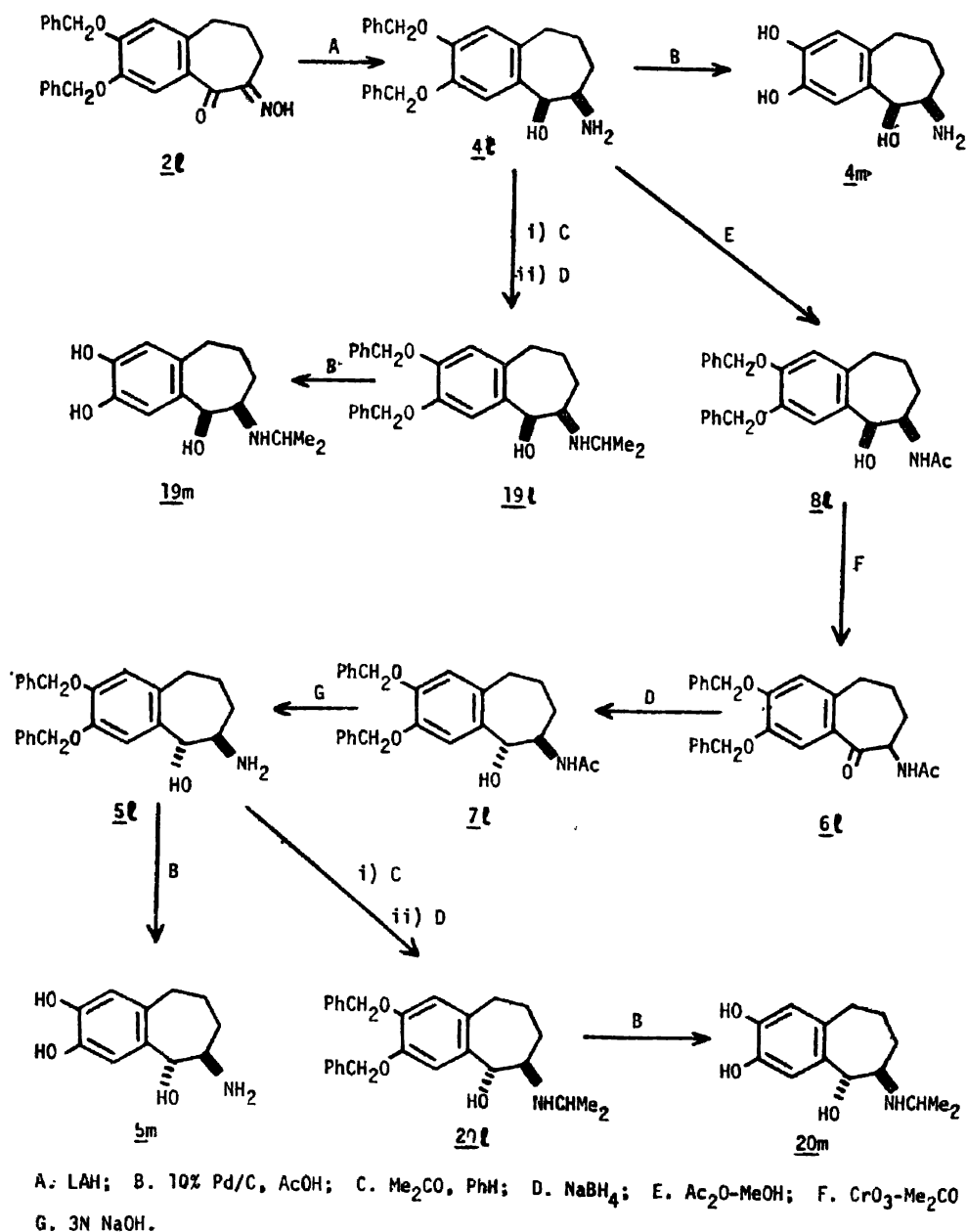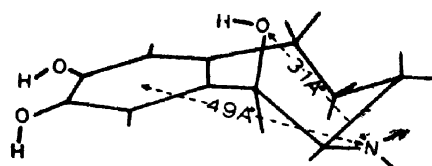G. 3N NaOH.

CHART V

mobility, or due to the 'induced fit' of the receptor. However, the benzocycloheptenol cannot change beyond the constraint of its ring structure and, therefore, it can be postulated with reasonable certainty that the structural profile of adrenergic structure must be such as would be able to associate with the following pattern (Fig. IV) of functionality presented by the agonist.

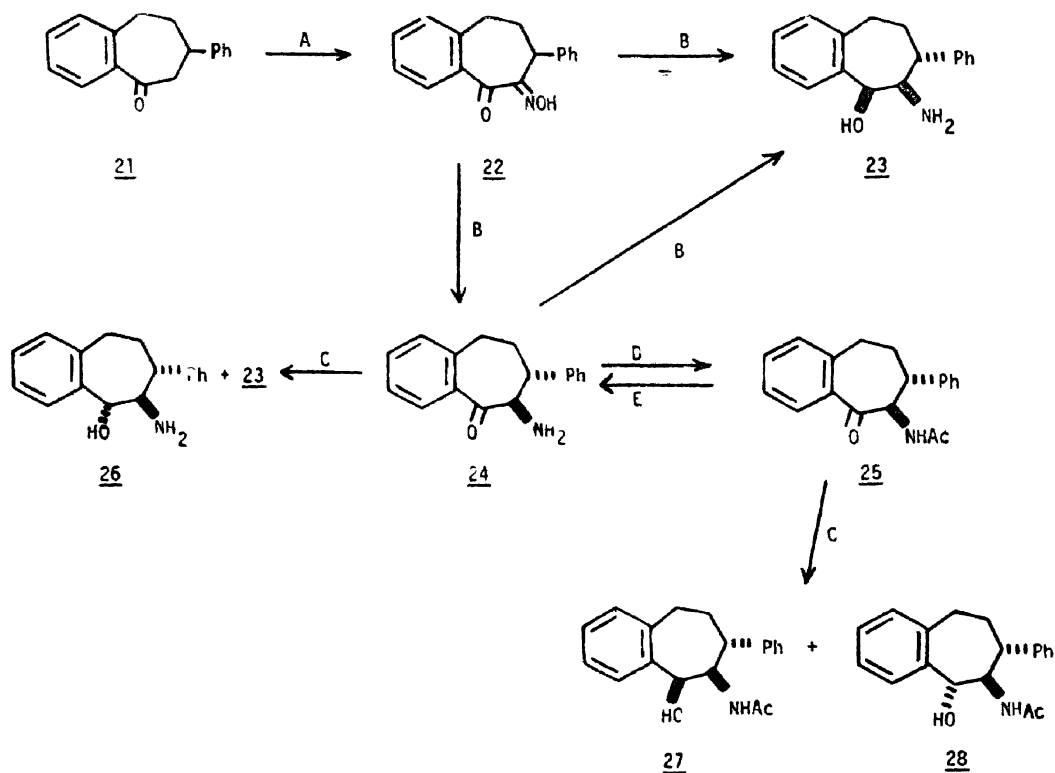III.   7-Phenyl-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols

5, 6-cis-(23)- and 5, 6-trans-(26)-6, 7-trans-7-phenyl-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocy-

CONFORMATION OF CIS-2,3-DIHYDROXY-6-AMINO-6,7,8,9,-
-TETRAHYDRO-5H-BENZOCYCLOHEPTEN-5-OL

FIG. IV

clohepten-5-ols[16] were synthesised according to the methods described in Chart VI.   Controlled catalytic

297

A. n-BuONO, KOEt or HCl; B. 10% Pd/C, MeOH, HCl; C. NaBH₄; D. Ac₂O-NaOAc-H₂O;
E. 3N HCl.

CHART VI

hydrogenation of 6-oximino-7-phenyl-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (22), gave 6, 7-trans-6-amino-7-phenyl-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (24). Further hydrogenation of 24 or complete hydrogenation of the oximino ketone 22 afforded exclusively 5, 6-cis-6, 7-trans-6-amino-7-phenyl-6, 7, 8, 9-tetrahydro-5H-benzocyclo-hepten-5-ol (23). NaBH₄ reduction of the amino ketone 24 gave 1:1 mixture of 5, 6-cis- and 5, 6-trans-6, 7-trans-7-phenyl-6-amino-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ols (23 and 26). Acid or base treatment of 5, 6-cis-6, 7-trans-6-amino-7-phenyl-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (23), its N-acetyl derivative 27 or O, N-diacetyl derivative 29 regenerated the 5, 6-cis-hydroxyamino compound 23, whereas acid treatment of 5, 6-trans-6, 7-trans-6-amino-7-phenyl-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-ol (26) or its N-acetyl derivative 28 gave 1:1 mixture of 5, 6-cis- and 5, 6-trans-hydroxyamino compounds 23 and 26 (Chart VII). In* about 8 hr over 40% epimerisation took place. This would indicate that the isomer 23 with 5, 6-cis-

stereochemistry is thermodynamically more favoured than the corresponding 5, 6-trans isomer 26.

**Stereochemical assignments**

The nmr spectrum of 24 showed a doublet at δ 5.2, J=8 Hz for H-6 and has, therefore, been assigned 6, 7-trans configuration with the ring in a half chair conformation (Fig. V), whereas in the nmr of the corresponding 6-acetamido ketone 25, H-6 appeared as a triplet collapsing to a doublet on deuteration, centred at δ 5.4 (J₆,₇=8 Hz). Another salient feature of nmr of the amino ketone 24 is the appearance of deformed triplet centred at δ 1.5 integrating for one proton, assigned to one of the 8-CH₂, undergoing geminal coupling. This upfield shift of one of the methylene proton was not observed in any other compound in this series. It appears that in the amino ketone 24, the amino and phenyl groups due to non-bonded interaction are locked and the 7-phenyl group is held in a plane perpendicular to the plane of the cycloheptene ring, which can cause shielding of one of the methylene protons. In 23

298
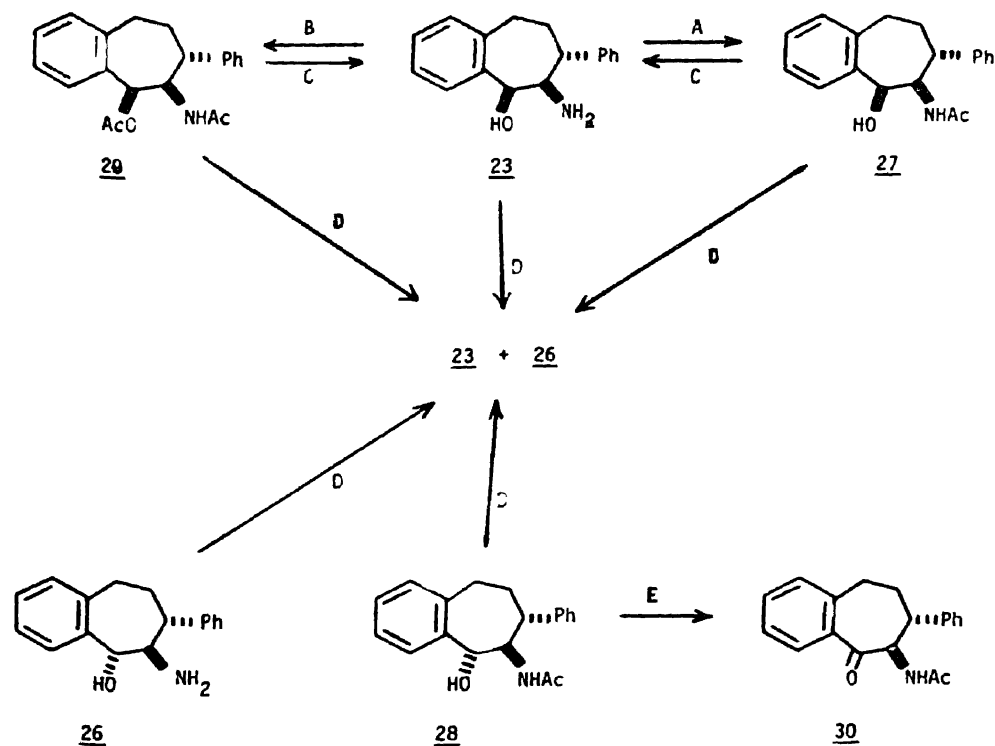
A. Ac_2O-MeOH; B. Ac_2O; C. 3N NaOH; D. 3N HCl; E. CrO_3, Me_2CO.

CHART VII


Ketoamino 24

Hydroxyamino 23

Hydroxyamino 26

FIG V
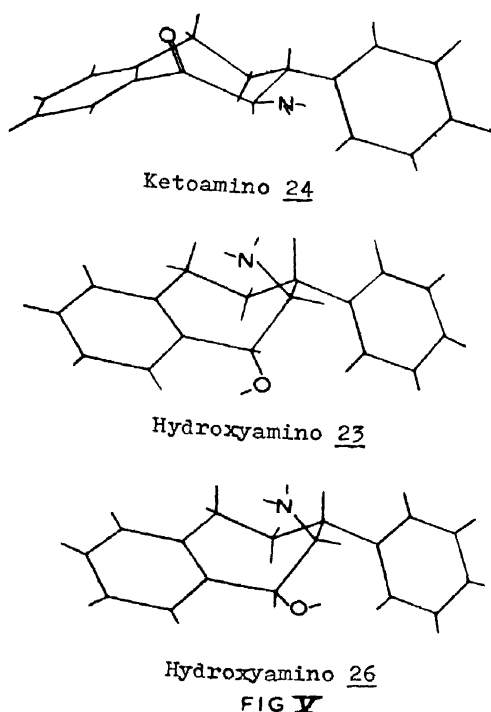
H-5 appeared as a broad singlet at δ 5.15 ($W\frac{1}{2}$ = 4 Hz) while in 26 this proton appears as a doublet at δ 4.85 (J=6 Hz) ; one of the aromatic protons in 23 was shifted considerably downfield. This peri-deshielding of the H-4 would require the 5-OH lying in the same plane as H-4 and this can happen only if 5-OH is equatorial. In both the isomers $J_{6,7}$ appears to be approximately 2, which is rather surprising as the starting ketoamino compound 24 had 6, 7-*trans* geometry with J=8 Hz. Epimerisation during catalytic reduction of 24 appeared very unlikely. Further confirmation for this came from the fact that 5, 6-*cis*-6, 7-*trans*-6-acetamido-benzo-cycloheptenol (27) on oxidation with Jone's reagent gave the original acetamidoketone 25 and its acid hydrolysis gave the aminoketone hydrochloride 24. In the aminobenzocycloheptenols 23 and 26 the 6, 7-substituents, therefore, must be *trans* as in the ketone 24. This change in 6, 7-*trans* coupling values, therefore, must involve a conformational change from a half chair to a twist boat form. It is proposed that 23 which has 5, 6-*cis*-6, 7-*trans* stereochemistry with 5-OH quasiequatorial has a twist-boat conformation

299

(Fig. V) with 7-phenyl quasi-equatorial. Similarly, 26 having 5, 6-trans-6, 7-trans stereochemistry has been assigned twist-boat conformation (Fig. V), in which the cycloheptene ring has the same conformation as for 23 and only 5-OH and H-5 are transposed. The reason for the conformational change of the amino ketone 24 on reduction from half chair to a twist boat conformation, is not very clear. In the likely conformation of hydroxyamino compounds, the 7-PH would be quasi-equatorial and the overall non-bonded interactions are not too unfavourable for this conformation and these factors may be responsible for this conformational change. From the above nmr data it appears that the conformation of cycloheptene ring is controlled by the substituents present in the cycloheptene ring.

IV. 10-Amino-10, 11-dihydro-5H-dibenzo(a, d) cyclohepten-11-ols[13]

cis-10-Amino-10, 11-dihydro-5H-dibenzo (a, d) cyclohepten-11-ol was prepared by catalytic hydrogenation of the oximinoketone 32 in MeOH-HCl using 10% Pd-C as catalyst (Chart VIII). If the hydrogenation was interrupted after the absorption of 1 mole of H₂, the amino-ketone 33 could be isolated ; further catalytic hydrogenation o⁻ NaBH₄ reduction of this ketone also gave exclusively the cis-aminodibenzocycloheptenol 34. Catalytic hydrogenation of 32 in presence of a mixture of AcOH and Ac₂O gave 10-acetamido-10, 11-dihydro-5H-dibenzo (a, d) cyclohepten-11-one, which on NaBH₄ reduction gave a 4:1 mixture (monitored by nmr
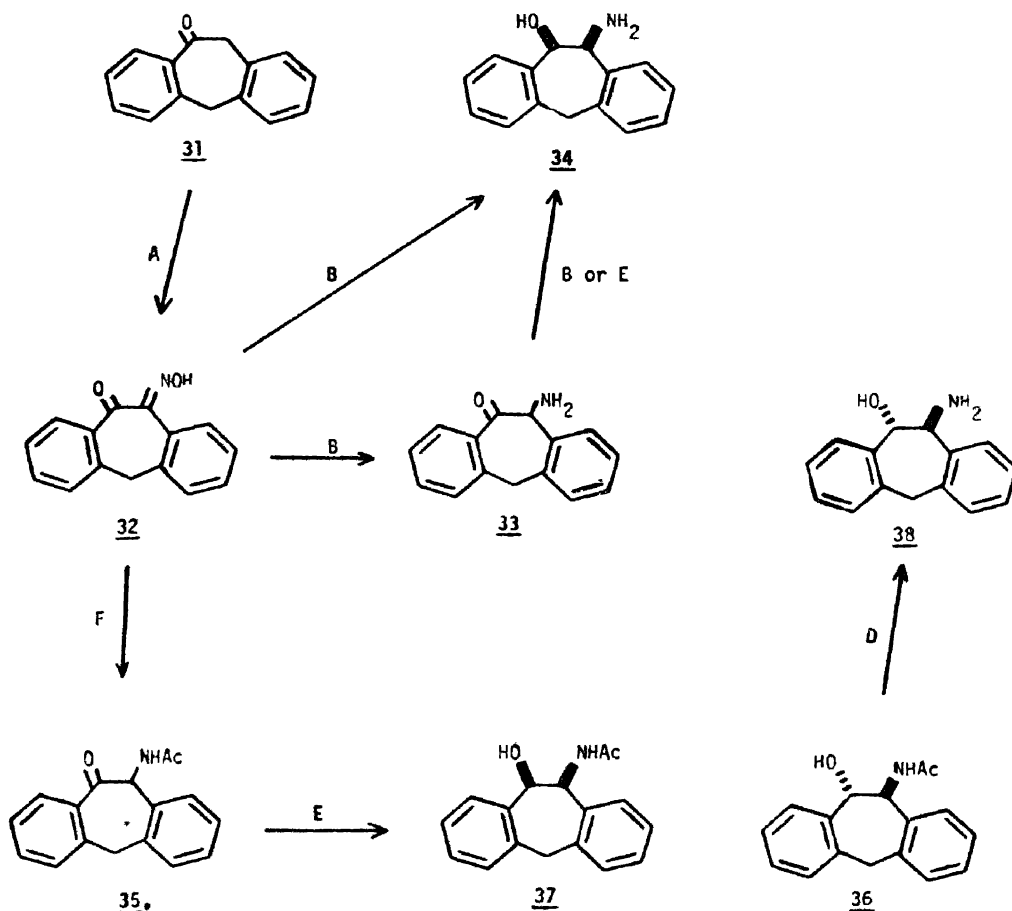
A. n-BuONO, KOEt or HCl; B. 10% Pd/C, MeOH, HCl; C. Ac₂O-MeOH; D. 3N NaOH;

E. NaBH₄; F. 10% Pd/C, Ac₂O-AcOH.

CHART VIII

spectroscopy) of the *cis*- and *trans*-10-acetamido-dibenzocycloheptenols *36* and *37* respectively. These could be easily separated by fractional crystallization or column chromatography. As in the case of aceta-midobenzocycloheptenols, it was found that both *36* and *37* gave the corresponding O-acetyl compound without inversion (the N→O acetyl migration was less facile in the case of *trans*-compound and about 40% of the N-acetyl compound was recovered) and NaHCO₃ treatment regenerated the acetamido compounds from the acetoxy derivatives (Chart IX). However, when either the *cis*- or *trans*-amino-diben-zocycloheptenols their N-acetyl or N, O-diacetyl derivatives were treated with 3*N* HCl under reflux for 30 min, a 1 :1 mixture of the *cis*- and *trans*-amino-dibenzocycloheptenols was formed. Base hydrolysis of the N-acetyl derivatives gave the corresponding aminodibenzocycloheptenols without affecting the stereochemistry.

N-acetyl derivatives of the mixture of the two epimers provide a convenient method for the preparation of the *trans*-compound *38*.

Stereochemical assignments

In the ir spectrum of *34* and *38* there was not much difference in the OH stretching vibration region, showing that the hydrogen bonding of the two iso-mers is of the same order. The pKa values of the two compounds also did not show much difference (*cis*, 7.75 ; *trans*, 7.85). In the nmr spectrum of the *cis*-isomer, there are two complementary doublets atδ 6.5 assigned to 10-H and atδ 5.75 assigned to 11-H with J=2.0 Hz ; in the *trans*-isomer, these doublets were present atδ 3.65 and δ4.23 with J= 9.0 Hz. The 5-CH₂ in both these compounds showed an AB pattern having J=15, thus showing that the two rings must be folded over and one of the methy-lene protons would be in the shielding cone of the ring.
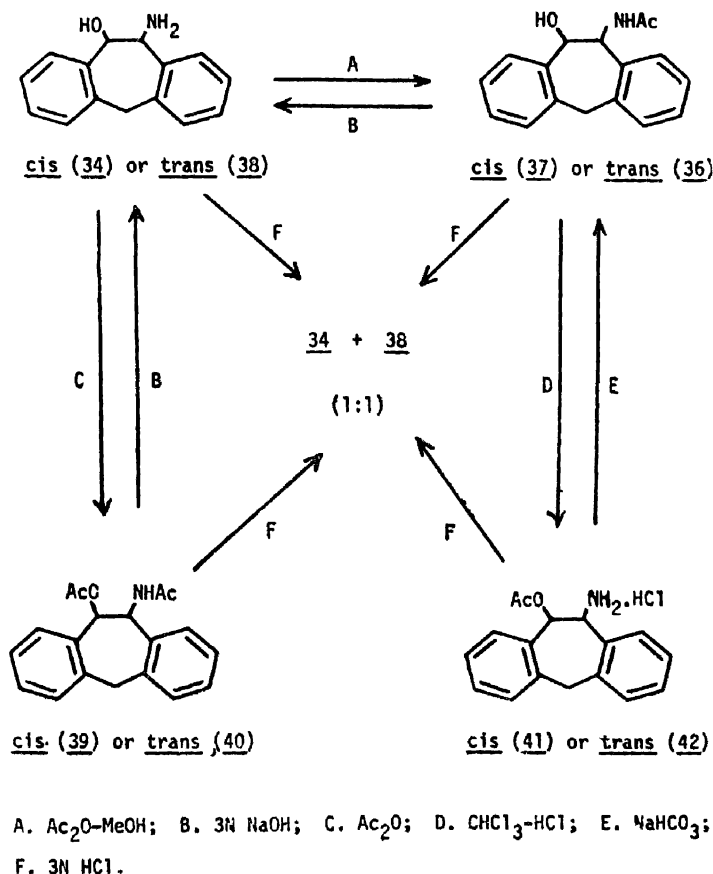

cis (**34**) or trans (**38**)

cis (**37**) or trans (**36**)

34 + **38**

(1:1)

cis· (**39**) or trans (**40**)

cis (**41**) or trans (**42**)

A. Ac₂O-MeOH; B. 3N NaOH; C. Ac₂O; D. CHCl₃-HCl; E. NaHCO₃;
F. 3N HCl.

CHART IX

As both catalytic and metal hydride reduction of the oximinoketone *32* and the amino ketone *33* gave exclusively the *cis*-isomer *34*, its facile epimerisa-tion by HCl treatment and easy separation of the

Biological activity

The *cis*-aminodibenzocycloheptenol (*34*) (LD₅₀ 290 mg/kg, mice, ip) in gross observation caused

sedation. At 30 mg/kg it showed marked analgesic action both by hot-plate and tail pinch screens. Dose for dose its activity was about 1/10th that of morphine and equivalent to that of pethidine, commonly used analgetics. At the analgesic dose, however, it caused neurologic deficit. It a'so had weak anticonvulsant activity. The corresponding trans-isomer (38) (LD₃₀ 75 mg/kg, ip, mice) had practically no analgesic or anticonvulsant activity.

V.   cis- & trans-4-Amino-2, 3, 4, 5-tetrahydro-1-benzoxepin-5-o [17]

4-Oximino-2, 3-dihydro-4H-1-benzoxepin-5-one (44) on cata'ytic hydrogenation formed 4-amino-2,

3-dihydro-4H-1-benzoxepin-5-one, which on further catalytic hydrogenation, NaBH₄ or LiAlH₄ reduction formed a mixture of cis- and trans-4-amino-2, 3, 4, 5-tetrahydro-1-benzoxepin-5-ol ; LiAlH₄ reduction of oximinoketone (44) also gave mixture of the two epimers (Chart X). The crude mixture on heating with Ac₂O in MeOH gave the corresponding N-acetyl derivatives which we-e separated by fractional crystallisation and hydrolysed with base to the corresponding cis- and trans-hydroxyamino compounds (46 and 47). Treatment of trans-4-amino-2, 3, 4, 5-tetrahydro 5H-benzocyclohepten-5-ol (47) with 3N HCl gave 1:1 mixture of cis- and trans-isomers, whereas cis-isomer 46 did not epimerise on treatment with 3N HCl.
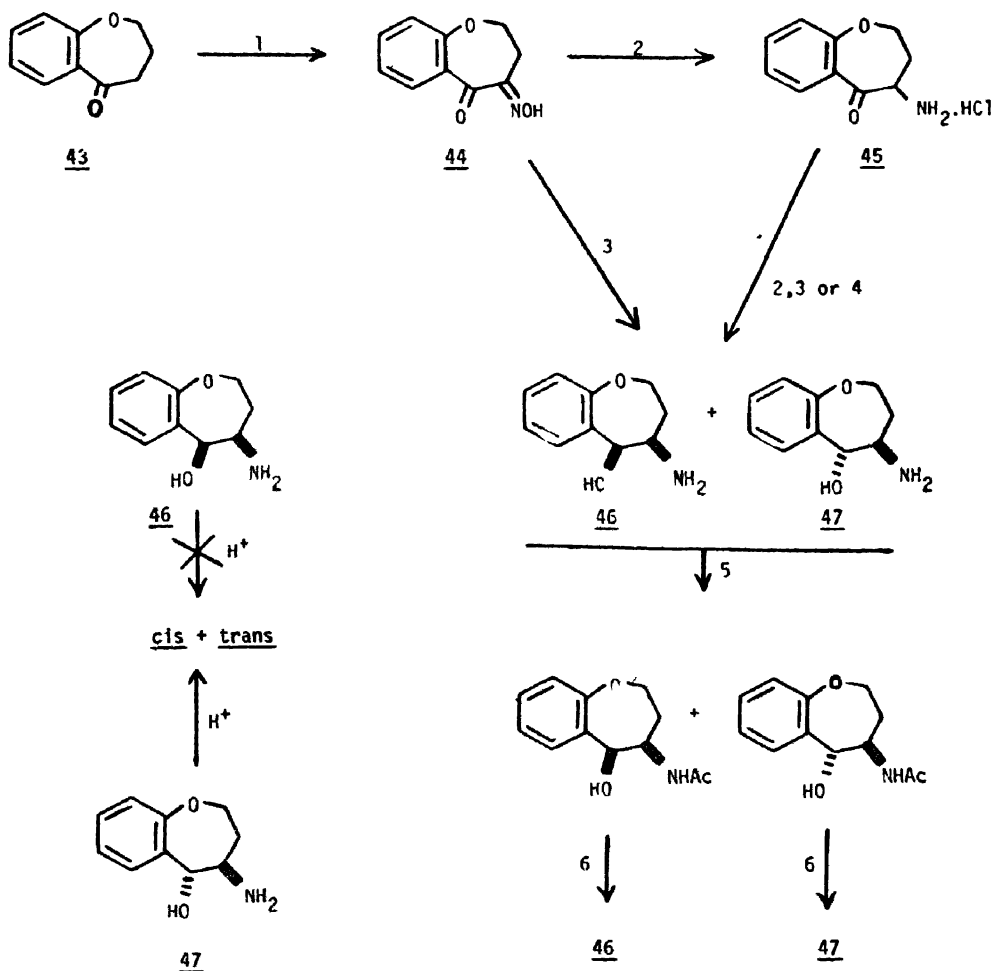
1. n/BuONO/KOEt;   2. 10% Pd/C, MeOH; HCl;   3. LiAlH₄;   4. NaBH₄

5. Ac₂O-MeCH;   6. 3N NaOH.

CHART X

Stereochemical assignments

In the nmr spectrum of *cis*-4-amino-2, 3, 4, 5-tetra-hydro-l-benzoxepin-5-ol, H-5 appeared at δ 4.85 (d, 1, J=9.0 Hz) and *trans* isomer, H-5 appeared at δ 4.6 (d, 1, J=9.0 Hz). The deshielding of aromatic H-6 was also observed in case of *trans* isomer.

References

1. J. M. KHANNA, J. BOLGER and N. Anand, *Indian J. Chem.*, 1969, **7**, 550.

2. J. M. KHANNA, B. LAL and N. ANAND, *J. Med. Chem.*, 1972, **15**, 23.

3. C. L. ANDERSON, W. J. HORTON, F. E. WALKER and M. R. WEILER, *J. Amer. Chem. Soc.*, 1955, **77**, 598.

4. A. M. KHAN, G. R. PROCTOR and L. REES, *J. Chem. Soc.*, 1966, 993.

5. E. E. GALANLARY, U. S., 3,458,577 ; *Chem. Abs.* 1969, **71**, 91170.

6. P. A. S. SMITH and W. L. BERRY, *J. Org. Chem.*, 1961, **26**, 27.

7. S. A. PATWARDHAN, *Indian J. Chem.*, 1969, **7**, 105.

8. G. FODOR and J. KISS, *J. Amer. Chem. Soc.*, 1950, **72**, 3495 ; 1952, **74**, 1589.

9. W. L. WELSH, *J. Org. Chem.*, 1967, **32**, 3295.

10. T. CHIEMPTASERT, H. RIMEK and F. ZYMALKOWSKY, *Ann.* 1964, **685**, 141.

11. N. LEVIN, B. E. GRAHAM and H. G. KOLLOFF, *J. Org. Chem.*, 1944, **9**, 380.

12. Merck Index (Merck & Co. Inc., U.S.A.) 1960, 869.

13. B. LAL, J. M. KHANNA and N. Anand, *Indian J. Chem.*, 1970, **8**, 1079.

14. B. LAL, J. M. KHANNA and N. ANAND, unpublished work.

15. B. LAL, J. M. KHANNA and N. ANAND, unpublished work.

16. B. LAL, J. M. KHANNA and N. ANAND, *Indian J. Chem.*, 1971, **9**, 1171.

17. V. K. TANDON, J. M. KHANNA and N. ANAND, unpublished work.