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Configuration and Conformation of So-called Bis(alkylidenearylamines)

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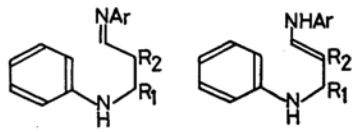
The proposed structures of the dimeric products obtained from aliphatic aldehydes and arylamines were reexamined by IR and NMR spectra. The 1,2,3,4-tetrahydroquinoline structure was ascertained in the case of acetaldehyde or propionaldehyde, and aldolic structure was confirmed in the case of *n*-butyraldehyde. It was observed that the latter readily isomerizes to the former type in the presence of acetic acid. Conformational analysis of a racemic pair of the former (IIIa—c: 2,4-disubstituted, IIId- 2,3,4-trisubstituted) indicated that two isomers of IIIa—c (one has 2-equatorial, 4-quasi-equatorial and the other 2-equatorial, 4-quasi-axial substituents) have a flattened half-chair conformation and two isomers of IIId (one has 2,3-diequatorial, 4-quasi-equatorial, and the other 2-equatorial, 3-axial, 4-quasi-axial substituents) have a more remarkably flattened half-chair, *i. e.* a nearly plane structure. The acylation of ring nitrogen enhanced this tendency, and one of the 1-acetyl derivatives of III was deduced to have a twist half-boat conformation.

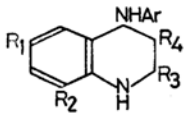
On the structure of so-called bis(alkylidene-arylamines) which have been regarded as one of the key-intermediates[1] in the Doebner-von Miller synthesis of quinolines from arylamines and aliphatic aldehydes, the following three formulas have been proposed; the acyclic structure of the aldol type (I), the enamine structure due to the isomerization of I (II) and the cyclic structure having 1,2,3,4-tetrahydroquinoline skelton (III).

1) N. Campbell, R. E. Fairbairn, E. Hoggarth, J. D. Loudon and T. S. Stevens, "Chemistry of Carbon Compounds," Vol. IV, ed. by E. H. Rodd and S. Coffey, Elsevier Publishing Company, Amsterdam, London, New York (1957), p. 588.



I II

$R_1 = CH_2CH_2CH_3$
$R_2 = CH_2CH_3$
$Ar = C_6H_5$



III

	R_1	R_2	R_3	R_4	Ar
a)	H	H	CH_3	H	C_6H_5
b)	CH_3	H	CH_3	H	4-Tolyl
c)	CH_3	CH_3	CH_3	H	2,4-Xylyl
d)	H	H	C_2H_5	CH_3	C_6H_5
e)	H	H	n-C_3H_7	C_2H_5	C_6H_5

Scheme 1

For a long time, structure I has been accepted without any definite evidences.[2] However, Minkin and Tumakoba[3] have recently proposed that, on the basis of IR and UV spectral investigation, both bis(ethylideneaniline) and bis(propylideneaniline) are of structure III, and bis(butylideneaniline), to which Kharasch *et al.*,[4] had given structure I, is of structure II.

In a previous paper,[5] the authors have reported the easy dimerization of *N*-phenyl-acetone-D-glyceraldimine to 4-anilino-1,2,3,4-tetrahydroquinoline derivatives in the presence of catalytic amount of acetic acid, and the determination of their partial absolute configuration by chemical degradation and spectral measurements.

These results stimulated us to determine the configuration and conformation of general bis(alkylidenearylamines) and their isomers by IR and NMR spectral studies, in connection with the mechanism of Doebner-von Miller reaction. The results obtained are discussed in this paper.

Results and Discussion

Configuration of Bis(alkylidenearylamines). The structures I, II, and III would be easily distinguished by the presence or absence of a characteristic absorption of C=C and C=N bonds in IR spectra, and azomethine and olefinic proton signals in NMR spectra. The results obtained indicated that bis(ethylideneaniline)[2] (IIIa), bis(ethylidene *p*-toluidine)[6] (IIIb), bis(ethylidene *m*-xylidine)[7] (IIIc) and bis(propylideneaniline)[2] (IIId) have structure III, because they showed the absence of C=C and C=N absorption band in IR spectra and the absence of azomethine and olefinic proton signals in NMR spectra, and furthermore, their monoacyl derivatives still showed the presence of NH absorption band at *ca.* 3300 cm^{-1}. The NMR spectra of these compounds will be shown and discussed in the next paragraph.

Contrary to Minkin's findings, NMR spectrum of bis(butylideneaniline) (I) shown in Fig. 1 indicated that it has aldol type structure. Irradiation of Ha caused Hc to collapse to a quartet, and reversal irradiation of Hc caused Ha to collapse to a seemingly narrow triplet with a long range coupling. Therefore, the quintet at τ 7.43, the quartet at τ 6.3 and the doublet at τ 2.2 (J=6.25) can be assigned to Hc, Hb and Ha, respectively.

The chemical shift of Ha is too low for that of olefinic proton and moreover, the coupling constants, which remained unchanged by addition of deuterium oxide, are too large to expect a long range coupling of the olefinic proton in structure II. The following examples of the chemical shifts of azomethine protons may also support the above conclusion; τ 1.65 in benzylideneaniline,[8] τ 2.37 in ethylidenepropylamine,[8] τ 2.56—3.16 in acetoaldoxime.[9] On the other hand, 2-ethylhexylideneaniline (IV), which is partially analogous to I and obtained from aniline and 2-ethylhexaldehyde, showed the presence of azomethine proton signal at τ 2.4 (J=6.5).

It has thus become clear that acetaldehyde or propionaldehyde give type III in the condensation with arylamines even in the absence of an acid catalyst, and a higher aldehyde such as *n*-butyraldehyde gives acyclic type I. In order to clarify such an effect of acid catalyst as was observed in a previous study[5] and the relationship between I and III, a catalytic amount of acetic acid was added to a solution of I in $CDCl_3$ (Fig. 2). The azomethine proton signal (Ha) disappeared promptly and a ring proton signal of 1,2,3,4-tetrahydroquinoline appeared at τ 5.62. This fact suggests the conversion of I to III, whose structure was also ascertained by UV (λ_{max} 251, 302 mμ) and IR (the disappearence of the absorption

2) W. v. Miller, J. Plöchl and F. Eckstein, *Ber.*, **25**, 1241, 2020 (1892); W. v. Miller and J. Plöchl, *ibid.*, **27**, 1299 (1894).

3) V. I. Minkin and Z. A. Tumakoba, *Zh. Obschch. Khim.*, **33**, 642 (1963); *ibid.*, **34**, 357 (1964).

4) M. S. Kharasch, J. Richlin and F. R. Mayo, *J. Am. Chem. Soc.*, **62**, 494 (1940).

5) M. Funabashi and J. Yoshimura, This Bulletin, **41**, 2735 (1968).

6) M. G. Edward, R. E. Garrod and H. O. Jones, *J. Chem. Soc.*, **1912**, 1383.

7) H. O. Jones and E. J. White, *ibid.*, **1910**, 632.

8) J. F. King and T. Durst, *Can. J. Chem.*, **40**, 882 (1962).

9) Varian's "NMR Spectra Catalog," Vol. 2.

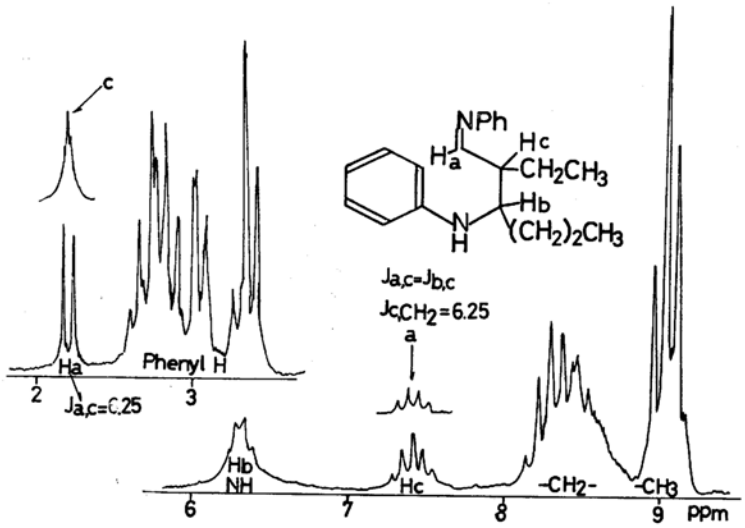


Fig. 1. NMR spectra of bis(butylideneaniline) (I) (100 Mc, $CDCl_3$).

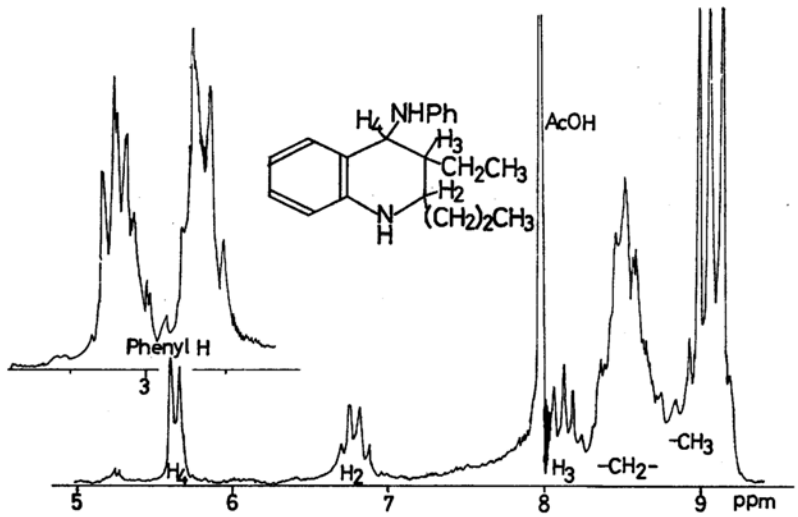


Fig. 2. NMR spectra of the isomerised compound (IIIe) of I in the presence of acetic acid (100 Mc, $CDCl_3$).

band of C=N and the increase of the intensity of the absorption band of NH), and moreover, by the fact that 1-tosyl derivative of IIIe still showed NH absorption band at 3300 cm^{-1}. Besides, distillation of I caused the β-elimination of aniline to give 2-ethyl-2-hexenylideneaniline (V). Such a phenomenon is characteristic for structure I, but not for III.

The Doebner-von Miller synthesis of quinolines from arylamines and lower aliphatic aldehydes has been done in a strongly acidic condition at a high temperature, and two reaction mechanisms[1] have been postulated for it; one includes the formation of α,β-unsaturated aldehydes due to the aldol condensation, the β-addition of arylamines and cyclization similar to that of the Skraup synthesis, and the other the intermediate such as I formed by the aldolic addition of alkylidenearylamines. The results described above seem to be closely related to the latter mechanism, and more detailed work is being undertaken.

Conformation of Bis(ethylidenearylamines) and Bis(propylidenearylamines). It is known that there are usually two isomers in bis-(ethylideneaniline). Some workers[10] considered them to be a pair of geometric isomers of structure II. However, it is now obvious that they should be the diastereomer of substituted 1,2,3,4-tetrahydroquinolines. Minkin and Gorelob[11] distinguished them from

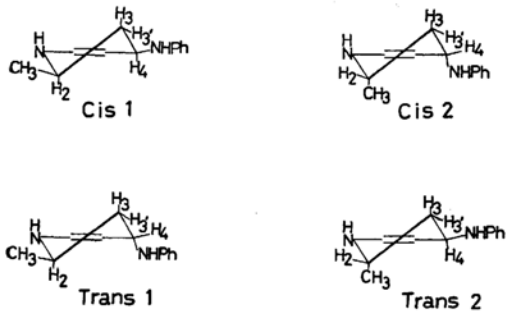
10) A. Eibner, *Ann.*, **318**, 58 (1901).

11) V. I. Minkin and M. I. Gorelob, *Zh. Obschch. Khim.*, **33**, 647 (1963); *Chem. Abstr.*, **59**, 2624f (1963).

their dipole moment, but the results are doubtful becasse of fundamental misunderstanding of stereochemistry. Therefore, the authors attempted to analyse the conformation of known and some new tetrahydroquinolines with NMR technique.

It has been concluded by X-ray analysis[12] that the cyclohexene molecule preferentially exists as a half-chair conformation, and the result has been applied to the conformational analysis of 1,2,3,4-tetrahydroquinolines,[13] glucal triacetate,[14] shikimic acid[15] and 1,2,3,4-tetrahydroisoquinolines.[16]

a) Conformation of Bis(ethylidenearylamines). Theoretically, there are two *cis* and two *trans* racemic stereoisomers, respectively in bis(ethylidenearylamines), *i. e.*, 1,2,3,4-tetrahydro-2,4-disubstituted-quinolines. Two substituents at C_2 and C_4 are equatorial and quasi-equatorial, or axial and quasi-axial in the case of *cis*-1 and *cis*-2, and equatorial and quasi-axial, or axial and quasiequatorial*1 in the case of *trans*-1 and *trans*-2, respectively.



Scheme 2

The order of the stability of four conformation will be empirically given as follows; *cis*-1, *trans*-1, *trans*-2 and *cis*-2. As has been pointed out by Booth[13] that the methyl group of 1,2,3,4-tetrahydro-2-methylquinoline prefers an equatorial orientation, it is probable that the favoured conformations of two known isomers of bis(ethylideneaniline) should be *cis*-1 and *trans*-1. The coupling constants of each ring protons, which can be calculated from the angle parameters of cyclohexene[17] and are listed in Table 1, make it possible to distinguish them. The order of the chemical shifts (τ) of ring protons will be given; H_3 (a), H_3' (e), H_2 and H_4 from higher to lower field.

TABLE 1. THE EXPECTED DIHEDRAL ANGLES[a] FOR 2,4-DISUBSTITUTED 1,2,3,4-TETRAHYDROQUINOLINES AND THE CORRESPONDING COUPLING CONSTANTS[b]

	(H_2, H_3)	(H_2, $H_{3'}$)	($H_{3'}$, H_4)	(H_3, H_4)
cis-1	178°	62°	45°	165°
J	14.2	2.7	6.2	13.4
	(11.0)	(3.0)	(7.1)	(10.0)
trans-1	178°	62°	75°	45°
J	14.2	2.7	0.83	6.2
	(11.0)	(3.0)	(0.77)	(7.1)
cis-2	62°	58°	75°	45°
J	2.7	2.8	0.83	6.2
	(3.0)	(3.0)	(0.77)	(7.1)
trans-2	62°	58°	45°	165°
J	2.7	2.8	6.2	13.4
	(3.0)	(3.2)	(7.1)	(10.3)

a) obtained from Bucourt's parameters
b) calculated from Abraham's equation[18] (Lemieux's equation[19])

The NMR spectrum of the one isomer of 1,2,3,4-tetrahydro-4-anilino-2-methylquinoline ($IIIa_1$, mp 126°C) is shown in Fig. 3. Inspection of this chart indicates that the $\delta\nu/J$ is sufficiently large to allow a first-order analysis. The quartet at τ 8.50, which is partly superimposed on the methyl proton signal, the octet at τ 7.67, the multiplet at τ 6.4, and the quartet at τ 5.2 are easily assigned to H_3 ($J_{3,3'}=J_{3,2}=J_{3,4}=11.5$ Hz), $H_{3'}$ ($J_{3',4}=5.0$, $J_{3',2}=2.5$ Hz), H_2 and H_4 respectively. Comparison of the above data with that of Table 1 clearly demonstrated that $IIIa_1$ belongs to *cis*-1 conformation. The dihedral angles of $IIIa_1$ are estimated from the equation of Abraham[18] as follows; (H_2, H_3)=(H_3, H_4)=155°, (H_2, $H_{3'}$)=63° and ($H_{3'}$, H_4)=51°.

The NMR spectrum of another isomer ($IIIa_2$, mp 86°C) is shown in Fig. 4. In this case, the sextet at τ 8.57 and τ 7.93, the multiplet at τ 6.63 and the quartet at τ 5.58 are assigned to H_3 ($J_{3,3'}=J_{2,3}=11.3$, $J_{3,4}=3.75$ Hz), $H_{3'}$ ($J_{2,3'}=J_{2',4}=2.5$ Hz), H_2 ($J_{2,CH_3}=6.5$ Hz) and H_4, respectively. The results indicate that $IIIa_2$ belongs to *trans*-1 conformation, and the dihedral angles are estimated in the similar manner: (H_2, H_3)=152°, (H_2, $H_{3'}$)=($H_{3'}$, H_4)=63° and (H_3, H_4)=58°.

The analytic data of IIIa, IIIb, IIIc and their 1-acyl derivatives, and 1,2,3,4-tetrahydro-2,6-dimethyl-4-hydroxyquinoline[2] (III'a; *trans*), 1,2,3,4-tetrahydro-1-acetyl-4-acetoxy-2,6-dimethylquinoline[2] (III'b; *cis*) and 1,2,3,4-tetrahydro-1-acetyl-4-ethoxy-2-phenylquinoline (III'c; *cis*) are summarized in Table 2. The ratio of the formation

*1 Axial, equatorial, quasi-axial and quasi-equatorial are abbreviated to a, e, qa and qe, respectively.

12) J. M. Lindsay and W. H. Barnes, *Acta Cryst.*, **8**, 227 (1955).
13) H. Booth, *J. Chem. Soc.*, **1964**, 1841.
14) L. D. Hall and L. F. Johnson, *Tetrahedron*, **20**, 883 (1968).
15) R. McCrindle, K. H. Overton and R. A. Baphael, *Tetrahedron Letters*, **1968**, 1847.
16) G. Grethe, M. Uskovic, T. Williams and A. Brossi, *Helv. Chim. Acta*, **50**, 2397 (1967).
17) R. Bucourt, *Bull. Soc. Chim. France*, **1964**, 2080; R. Bucourt and D. Hainaut, *ibid.*, **1965**, 1366.
18) R. J. Abraham, *Mol. Phys.*, **5**, 513 (1962).
19) R. U. Lemieux and W. J. Lown, *Can. J. Chem.*, **42**, 893 (1964).

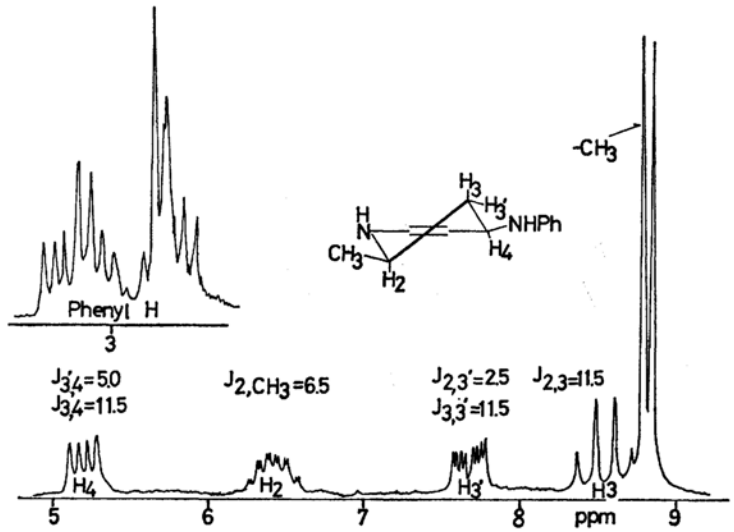


Fig. 3. NMR spectrum of 1,2,3,4-tetrahydro-4-anilino-2-methylquinoline ($IIIa_1$) [bis(ethylideneaniline):*cis*] (100 Mc, $CDCl_3$).

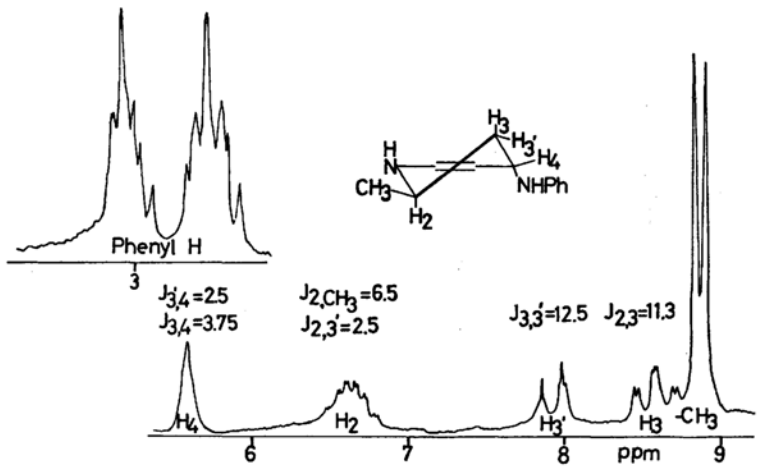


Fig. 4. NMR spectrum of 1,2,3,4-tetrahydro-4-anilino-2-methylquinoline ($IIIa_2$) [bis(ethylideneaniline):*trans*] (100 Mc, $CDCl_3$).

of $IIIa_1$ and $IIIa_2$ in the crude product was estimated from the intensity of each H_4 proton signal, to be 1 : 1, whereas, in the case of IIIc, *trans*-1 type was preferentially formed. The latter case will be probably due to the allylic strain[20] between the carbon atom at C_5 and *m*-xylidine residue at C_4 bulkier than phenyl.

The phenomenon that the spiltting number of the methylene proton in 4-ethoxy group of III'c is not a quartet, but a double quartet, suggests the presence of such a hindrance.

The fact that the dihedral angles (H_2, H_3) and (H_3, H_4) are less than that of cyclohexene indicates a considerable flattening of the typical half-chair conformation. A more remarkable tendency to flatten the conformation has been observed in the case of 1-acyl derivatives of IIIa, IIIb and IIIc, in which the coupling constants between H_2 and H_3 are generally smaller than those of the parent compounds. For example the coupling constant: $J_{2,3}$ (7.5 Hz) of 1-acetyl derivative of IIIc indicates the decrease of the angle from 156° to 136°. This change will be attribuable to the 1,2-skew interaction of acetyl group at C_1 and methyl group at C_2, and also to the allylic strain between acetyl group and methyl group at C_8.

As a general tendency of the NMR data (see Table 2), H_4 proton (qa) of 1-acyl derivatives of *cis*-1 type shifts to a higher magnetic field than H_4 proton of the parent compounds free of acyl group.

20) F. Johnson, *Chem. Revs.*, **68**, 378 (1968).

However, it is scarcely changed in the case of *trans*-1 type. H_3 proton also indicates a similar tendency. The former case is consistent with the report of Lambert[21] *et al.*, in which they indicated that the anticoplanarity between H_7 proton and axial lone pair electron of nitrogen atom in the *N*-substituted piperidine ring causes the chemical shift of H_7 (τ) to a higher magnetic field.

b) Conformation of Bis(propylidenearylamines). In the case of bis(propylidenearylamines), *i. e.*, 1,2,3,4-tetrahydro-4-anilino-2-ethyl-3-methylquinoline, eight half-chair conformations of racemic diastereoisomers are theoretically possible, and among them, the most favored ones will be the two having C_2-e, C_3-e, C_4-qe or C_2-e, C_3-e, C_4-qa substituents. Miller *et al.*[2] have found only one isomer ($IIId_1$; mp 103°C). However, another one should exist as in the case of bis(ethylideneaniline), and in fact, we have succeeded in isolating one ($IIId_2$) as a syrup from the mother liquor of $IIId_1$. The IR spectrum of $IIId_2$, which is very similar to that of $IIId_1$, showed absence of C=C or C=N absorption band, and that of 1-acyl derivative of $IIId_2$ still showed NH absorption band at 3320 cm^{-1}.

In the NMR spectrum of $IIId_1$ shown in Fig. 5,

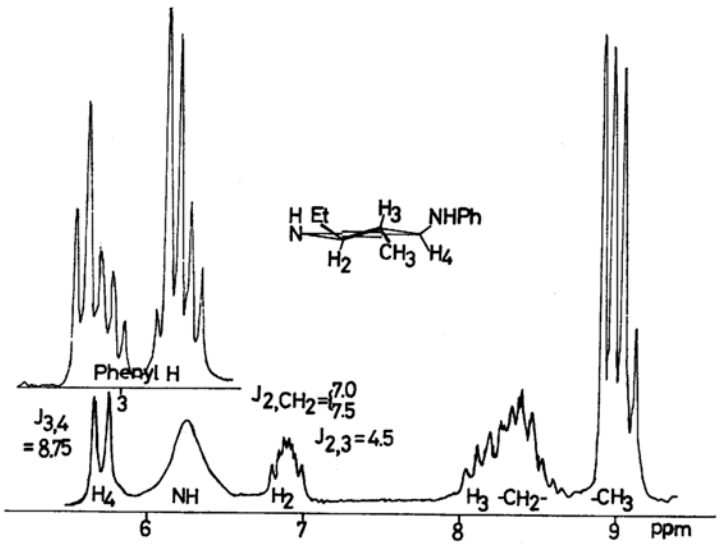


Fig. 5. NMR spectrum of 1,2,3,4-tetrahydro-4-anilino-2-ethyl-3-methylquinoline ($IIId_1$) [bis(propylideneaniline): 2,4-*cis*] (100 Mc, $CDCl_3$).

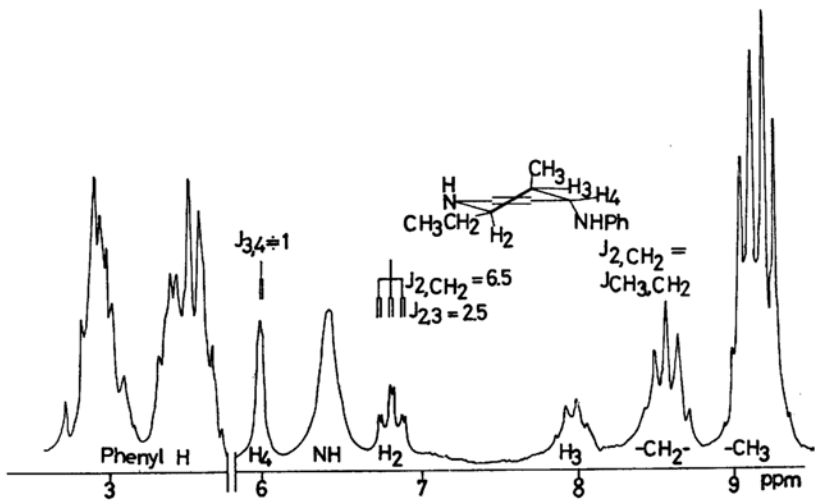


Fig. 6. NMR spectrum of 1,2,3,4-tetrahydro-4-anilino-2-ethyl-3-methylquinoline ($IIId_2$) [bis(propylideneaniline): 2,4-*trans*] (100 Mc, $CDCl_3$).

21) J. B. Lambert, R. G. Keste, R. E. Carhart and A. P. Javanovich, *J. Am. Chem. Soc.*, **89**, 3761 (1967).

TABLE 2. FIRST-ORDER ANALYSIS OF NMR SPECTRA OF 2,4-DISUBSTITUTED 1,2,3,4-TETRAHYDROQUINOLINES

	Chemical shifts (τ)						Coupling constants (Hz) (dihedral angles)					
	H_2	$H_{3'}$	H_3	H_4	CH_3	$=NCOCH_3$	$J_{2,3}$	$J_{2,3'}$	$J_{3,3'}$	$J_{3,4}$	$J_{3,4}$	J_{2,CH_3}
$IIIa_1$ (*cis*)	6.30 m*	7.67 o	8.55 q	5.20 q	8.82 d	—	11.5 (155°)	2.5 (63°)	11.5	5.0 (51°)	11.5 (155°)	6.5
$IIIa_2$ (*trans*)	6.50 m	7.86 dt	8.49 o	5.45 q	8.80 d	—	11.3 (152°)	2.5 (63°)	12.5	2.5 (63°)	3.75 (58°)	6.5
1-acetyl of $IIIa_1$	5.04 m	7.33 o	ca. 8.7 s	5.75 q	8.83 d	7.80	7.0 (134°)	8.75 (33°)	12.5	4.5 (53°)	12.5 (159°)	7.0
1-benzoyl of $IIIa_1$	5.12 m	7.23 dt	8.64 dt	5.56 t	8.73 d	—	8.0 (139°)	9.2 (30°)	12.5	5.0 (51°)	11.3 (152°)	6.5
1-benzoyl of $IIIa_2$	5.19 m	7.58 dt	8.1 dt	5.33 t	8.72 d	—	6.5 (132°)	6.5 (43°)	12.5	5.0 (51°)	5.0 (51°)	7.0
IIIb (*cis*)	6.45 m	7.60 o	8.55 q	5.25 q	8.83 d	—	11.3 (152°)	—	11.3	5.0 (51°)	11.3 (152°)	6.0
1-acetyl of IIIb	5.19 m	7.38 o	ca. 8.8 s	5.89 q	8.90 d	7.92	11.3 (152°)	—	12.5	4.0 (56°)	11.5 (155°)	6.5
IIIc (*trans*)	6.50 m	—	8.50 o	5.45 q	8.76 d	—	12.0 (157°)	—	12.0	2.5 (63°)	3.5 (58°)	6.3
1-acetyl of IIIc	4.85 s	7.31 o	8.61 o	5.52 q	8.94 d	7.80	7.5 (136°)	7.5 (38°)	12.5	2.5 (63°)	4.0 (56°)	7.5
III'a** (*trans*)	6.57 m	8.07 dt	8.55 dt	5.39 q	8.83 d	—	12.0 (157°)	2.5 (54°)	13.7	2.5 (63°)	3.5 (58°)	6.25
III'b (*cis*)	5.08 m	7.40 o	8.52 o	4.28 q	8.83 d	7.62	7.0 (134°)	7.0 (41°)	12.5	5.0 (51°)	10.0 (147°)	6.0
III'c (*cis*)	4.30 m	7.06 o	8.36 dt	5.65 q	—	7.87	10.0 (147°)	10.0 (26°)	12.0	3.75 (58°)	12.0 (157°)	—

* d=doublet, dt=double triplet, m=multiplet, o=octet, q=quartet, s=sextet, t=triplet. ** IIIa'; 1,2,3,4-tetrahydro-2,6-dimethyl-4-hydroxyquinoline, IIIb'; 1,2,3,4-tetrahydro-4-acetoxy-1-acetyl-2,6-dimethylquinoline, IIIc'; 1,2,3,4-tetrahydro-1-acetyl-4-ethoxy-2-phenylquinoline.

TABLE 3. FIRST-ORDER ANALYSIS OF NMR SPECTRA OF 2,3,4-TRISUBSTITUTED 1,2,3,4-TETRAHYDROQUINOLINES

	Chemical shifts (τ)							Coupling constants (Hz) (dihedral angles)				
	H_2	H_3	H_4	CH_3-C_3	CH_2-CH_3	CH_2CH_3	$=NCOCH_3$	$J_{2,3}$	$J_{3,4}$	J_{2,CH_2}	J_{3,CH_3}	$J_{CH_2-CH_3}$
$IIId_1$	6.90 o	8.17 m	5.72 d	8.95 d	8.40 m	9.06 t		4.5 (124°)	8.75 (142°)	7.0 7.5	6.3	7.0
$IIId_2$	6.80 dt	7.97 m	5.95 d	9.07 d	8.57 m	9.18 t		2.5 (63°)	ca. 1 (74°)	6.5	5.0	6.5
1-acetyl of $IIId_1$	5.39 m	8.5 m	6.07 d	8.73 d	ca. 8.5 m	9.15 t	7.80	7.0 (134°)	9.0 (143°)	—	6.5	7.0
1-aectyl of $IIId_2$	5.29 m	8.37 m	5.65 d	8.87 d	ca. 8.7 m	9.10 t	7.72	3.5 (58°)	11.3 (17°)	7.0	7.50	7.0

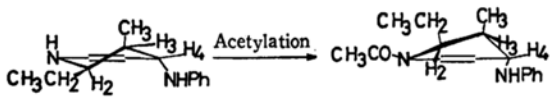
the multiplet at *ca.* τ 8.2, which is partly superimposed on C_3 methyl proton signal, the octet at τ 6.90 and the doublet at τ 5.72 are assigned to H_3 ($J_{2,3}$=4.5 Hz), H_2 (J_{2,CH_2}=7.0, 7.5 Hz) and H_4 ($J_{3,4}$=8.75), respectively. The irradiation of H_3 caused H_4 proton signal to collapse to a singlet. The coupling constants mentioned above roughly support the fact that the substituents of $IIId_1$ at C_2, C_3 and C_4 are e, e and qe. The dihedral angles of ring protons; (H_2, H_3)=124° and (H_3,H_4) =141° indicate a more remarkably flattened half-chair (rather plane) conformation than that of IIIa.

In the NMR spectrum of the other isomer ($IIId_2$) shown in Fig. 6, a multiplet centered at τ 7.97, a triplet doublet at τ 6.80 and a narrow doublet at τ 5.95 are assigned to H_3, ($J_{2,3}$=2.5 Hz), H_2 (J_{2,CH_2}=6.5 Hz) and H_4 ($J_{3,4}$=*ca.* 1 Hz), respectively. The dihedral angles are similarly estimated to be (H_2, H_3)=114° or 64° and (H_3, H_4)=105° or 74°. The most profitable conformation to be justified by these angles is a flattened half-chair having C_2-e, C_3-a and C_4-qa substituents or a rather contracted half-boat conformation having C_2-e, C_3-e and C_4-qa substituents, but not a half-chair having C_2-e, C_3-e and C_4-qa which was mentioned above as a stable one. Among the two probable conformations, however, the latter is not adoptable because of the instability factor due to the constraction strain. Therefore, the former is preferable to $IIId_2$.

This conclusion will be supported by the following considerations. If $IIId_1$ and $IIId_2$ can be formed through the structure of type I, as in the case in which I cyclizes to IIIe, racemic *threo* and *erythro* isomers of type I should exist in the intermediate step. The *threo* isomer will preferentially cyclize to the conformation having C_2-e and C_3-e substituents. However, the *erythro* isomer should give a half-chair conformation having C_2-a or C_3-a substituent. Though C_4 configuration can not be estimated unless the transition state of such a cyclization is clarified, we can understand that $IIId_1$ is preferentially formed, so far as stability is concerned. However, in the case of *erythro*, two stable conformations are equally possible from the standpoint of the nonbonded interaction. The following consideration may be allowed: there are four possible conformations to be formed by the cyclization of the *erythro* intermediate;

A) C_2-a, C_3-e and C_4-qe, B) C_2-a, C_3-e and C_4-qa, C) C_2-e, C_3-a and C_4-qe, D) C_2-e, C_3-a and C_4-qa. The instability factor of the substituents can be roughly estimated as follows: A; 3 skews (C_2-a and C_3-e, C_2-a and C_3-C_4 bond, C_3-e and C_4-e), B; 4 skews (C_2-a and C_3-e, C_2-a and C_3-C_4 bond, C_4-a and C_3-e, C_4-a and C_2-C_3 bond) and 1,3-diaxial interaction (C_2-a and C_4-a), C; 4 skews (C_3-a and C_2-e, C_3-a and C_2-N bond, C_3-a and C_4-e, C_3-a and C_4-$C_{benzene}$), and D; 4 skews (C_3-a and C_2-e, C_3-a and C_4-$C_{benzene}$, C_3-a and C_2-N bond, C_4-a and C_2-C_3 bond), respectively. Among these skew interactions, C_2-a and C_3-C_4 bond, C_3-e and C_4-e, C_3-a and C_2-N bond, C_3-a and C_4-$C_{benzene}$, C_4-a and C_2-C_3 bond interactions will be weakened by flattening of half-chair conformation (enlargement of the dihedral angles), and others will be enhanced because of the eclipse effect of the substituents. Therefore, both A and D conformations are almost equivalent with respect to the instability factor. The A conformation, however, is rejected so far as NMR is concerned, because the coupling constant ($J_{3,4}$) of $IIId_2$ is too small (*ca.* 1 Hz) for that of A conformation (H_3 and H_4; *trans*-diaxial). Accordingly, D conformation is preferable to $IIId_2$.

The formation ratio of $IIId_1$ (*threo*) and $IIId_2$ (*erythro*) was measured from the intensity of each H_4 protons in the crude mixture to be 55 : 45. The coupling constants of ring protons of acetyl derivatives of $IIId_1$ and $IIId_2$ shown in Table 3 indicate that the conformation of $IIId_1$ remained almost unchanged. However, $J_{3,4}$ value of $IIId_2$ changed remarkably from *ca.* 1 to 11.3. This change may be explained by the conversion of the conformation from half-chair to a twisted half-boat or by the conversion to A conformation, in order to avoid 1,2-interaction between acetyl and ethyl group.



$IIId_2$

Scheme 3

On the other hand, the NMR data in Table 3 indicate that H_4 proton of 1-acetyl derivative of $IIId_1$ (2,4-*cis*) shifts to a higher magnetic field than that of $IIId_1$ as in the case of IIIa or IIIb. This phenomenon may be of use for the conformational analysis of 4-, or 2,4- or 2,3,4-substituted 1,2,3,4-tetrahydroquinolines and others.

A general conclusion may be given for the conformation of the substituted 1,2,3,4-tetrahydroquinolines that; 1) 2,4-disubstituted 1,2,3,4-tetrahydroquinolines have a flattened half-chair conformation (C_2-e, C_4-qe or C_2-e, C_4-qa). 2) 2,3,4-Trisubstituted 1,2,3,4-tetrahydroquinolines have a remarkably flattened half-chair or twisted half-boat conformation (C_2-e, C_3-e and C_4-qe or C_2-e, C_3-a and C_4-qa). 3) 1-Acyl derivatives of the substituted 1,2,3,4-tetrahydroquinolines have a more flattened half-chair than the acyl free derivatives.

Experimental

All the aliphatic aldehydes and arylamines were purified before use by distillation of the commercial

products. The melting points were uncorrected. The measurements of NMR spectra were effected with JEOL JNM-4H-100 in deuteriochloroform by using TMS as an internal reference. IR spectra were measured with Hitachi EPI-G2. UV spectra were measured with Hitachi EPS-3T in methanol solution. TLC was carried out on layers of silica gel (WAKO-GEL B-Q) on glass plates, using benzene (system A) or benzene-ligroin (3 : 1, system B) as developers and 2% aqueous potassium permanganate-sodium carbonate or chromic-sulfuric acid (5%-$K_2Cr_2O_7$ in 40% H_2SO_4) as spray reagents. R_a value is the rate of movement of the 1,2,3,4-tetrahydroquinolines relative to aniline.

Bis(butylideneaniline) (I : 3-anilino - 2 - ethylhexylideneaniline). Equimolar amount of freshly distilled aniline and *n*-butyraldehyde was mixed and allowed to stand at room temperature for 24 hr according to the method of Kharasch *et al.*[4] White crystals were obtained in a yield of 55%. Mp 92°C (lit, 92.5°C). I in an alcoholic solution gradually isomerized to 1,2,3,4-tetrahydro-4-aniline-3-ethyl-2-propylquinoline (IIIe) and the yield decreased.

1,2,3,4-Tetrahydro-4-anilino-3-ethyl-2-propylquinoline (IIIe). To a solution of bis(butylideneaniline) (I: 2.94 g, 10 mmol) dissolved in chloroform (10 m*l*) was added two drops of acetic acid and the solution was allowed to stand at room temperature overnight, neutralized with an aqueous sodium hydrogene carbonate, washed with water and dried over Na_2SO_4. Evaporation of chloroform gave a pale yellow syrup (2.9 g), which shows no absorption band of imine at *ca.* 1650 cm^{-1}. UV: λ_{max}^{MeOH} 251 mμ ($\log \varepsilon$=4.43), 302 mμ ($\log \varepsilon$=3.87).

1-Tosyl Derivative of IIIe. IIIe was tosylated with *p*-toluenesulfonyl chloride (1.2 times mole of IIIe) in pyridine in an usual manner to give 1,2,3,4-tetrahydro-4-anilino-3-ethyl-2-propyl-1-tosylquinoline in a yield of 22% (crystals). Mp 210—211°C (recrystallized from acetone). IR; 3400 cm^{-1} (NH), 1340, 1162cm^{-1} (*N*-tosyl).

Found: C, 72.04; H, 7.33; N, 6.50; S, 7.42%. Calcd for $C_{27}H_{32}O_2N_2S$ (448): C, 72.29; H, 7.19; N, 6.29; S, 7.15%.

2-Ethyl-1-hexylideneaniline (IV). 2-Ethylhexaldehyde (12.8 g, 0.1 mol) was added to aniline (9.3 g, 0.1 mol) with cooling in an ice-water and the mixture was allowed to stand at room temperature overnight. After drying over Na_2SO_4, distillation of the reaction product was effected under 1 mmHg to give a pale yellow oil (15.8 g, 77.6%). Bp 92—95°C/1 mmHg.

Found: C, 82.75; H, 10.19; N, 6.76%. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89%.

Pyrolysis of Bis(butylideneaniline)(I) to 2-Ethyl-2-hexenylideneaniline (V). I (3 g, 10.2 mmol) was filled in a sealed tube and heated in an oil bath at 120—140°C for 12 hr. Distillation of the reaction product *in vacuo* gave an oil (V) (1.5 g, 74%) having bp 142—147°C/11 mmHg (lit,[4] 146—148°C/15 mmHg). Refluxing of the acidic ethanol solution of V with 2,4-dinitrophenylhydrazine for 2 hr gave 2,4-dinitrophenylhydrazone (red crystals). Mp 118°C (lit,[4] 119—120°C).

Bis(ethylideneaniline) (1,2,3,4 - Tetrahydro - 4 - anilino-2-methylquinoline: $IIIa_1$ and $IIIa_2$). $IIIa_1$ (*cis*) and $IIIa_2$ (*trans*) were prepared from aniline (0.1 mol) and acetaldehyde (0.1 mol) in a mixture of ethanol (150 m*l*) and water (100 m*l*) in a yield of 20% ($IIIa_1$) and 22% ($IIIa_2$), respectively, by the Method of Minikin and Tumakoba.

$IIIa_1$: mp 121—124°C (lit,[2] 126°), R_a 1.64 (system A).

$IIIa_2$: syrup (lit,[2] 85.5°), R_a 2.07 (system A).

(Found of $IIIa_2$: C, 80.45: H, 7.92; N, 11.40%. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.78%).

1-Acetyl derivative of $IIIa_1$. To a solution of $IIIa_1$ (0.3 g, 1.26 mmol) in pyridine (2 m*l*), acetic anhydride (1 g, 10 mmol) was added and the mixture was allowed to stand at room temperature for 2 days, and then poured into ice-water. The precipitated crystalline products were filtered, washed with water, dried and recrystallized from ethanol. Yield, 0.3 g (84.6%). Mp 110.5—111°C.

Found: C, 77.40; H, 6.92; N, 9.52%. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99%.

1-Benzoyl derivative of $IIIa_1$: mp 216—217°C (lit,[2] 218°C).

1-Benzoyl derivative of $IIIa_2$: mp 156—157°C (lit,[2] 186°C).

Bis(ethylidene *p*-toluidine) [1,2,3,4-Tetrahydro-2,6-dimethyl-4-(*p*-toluidino)quinoline: IIIb]. IIIb (*cis*) was prepared by the method of Jones *et al.*[6] in a yield of 43%. Mp 113—114°C (lit, 114—116°C).

1-Acetyl derivative of IIIb; mp 141—143°C, yield 57.5%.

Found: C, 77.38; H, 7.65; N, 8.74%. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.85; N, 9.08%.

Bis(ethylidene *m*-xylidine) [1,2,3,4-Tetrahydro-2,6,8 - trimethyl - 4 - (*m*-xylidino)quinoline: IIIc]. IIIc was prepared by the method of white *et al.*[8] in a yield of 97%. Mp 141—143°C (lit, 145°C). 1-acetylation was difficult probably because of the steric hindrance due to the 8-methyl group. Yield, 15%. Mp 142—143°C (lit, 145°C).

1,2,3,4-Tetrahydro-4-hydroxy-2,6-dimethylquinoline (III'a : *trans*): mp 107.5—110°C (lit,[2] 108—110°C).

1,2,3,4-Tetrahydro-4-acetoxy -1- acetyl-2,6 - dimethylquinoline (III'b : *cis*): mp 119—119.5°C (lit,[2] 117—119°C).

1,2,3,4-Tetrahydro -1- acetyl -4- ethoxy -2- phenylquinoline (III'c : *cis*). A mixture of 1,2,3-4-tetrahydro-4-ethoxy-2-phenylquinoline[22] (1 g, 3.93 mmol), acetic anhydride (10 m*l*) and pyridine (1 m*l*) was refluxed for 15 min, allowed to stand at room temperature for 2 hr and then poured into ice-water. Precipitated oil was extracted with chloroform, and organic layer was neutralized with aqueous $NaHCO_3$, washed with water and dried over Na_2SO_4. Evaporation of chloroform gave a syrup, which was purified with a silica gel column (WAKO-GEL Q-50). From the fraction of benzene and benzene-acetone (10:1), crystalline product was obtained in a yield of 53%. Mp 120—121°C.

Found: C, 76.89; H, 6.83; N, 4.57%. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74%.

Bis(propylideneaniline) (1,2,3,4 - Tetrahydro - 4 - anilino-2-ethyl-3-methylquinoline: $IIId_1$ and $IIId_2$). To a cold solution of aniline (9.3 g, 0.1 mol) in ethanol (25 m*l*), propionaldehyde (5.8 g, 0.1 mol) was added and

22) V. I. Grigos, L. S. Povarov and B. M. Mikhailov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **1965**, 2163; *Chem. Abstr.*, **64**, 9680c (1966).

the reaction solution was allowed to stand in a refrigerator for 2 days. The white crystalline mass was filtered and the crude product ($IIId_1$, 4.8 g) was recrystallized from ethanol. Mp 104—105°C (lit,[2] 103°C), R_a 2.46 (system B). The mother liquor, scarcely containing any $IIId_1$, was evaporated *in vacuo* to a syrup ($IIId_2$, 5.2 g) and the small amount of remaining aniline was distilled off. R_a 2.88 (system B).

Found: C, 80.99; H, 8.31; N, 11.42%. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.33; N, 10.52%.

Acetylation of $IIId_1$ and $IIId_2$ with acetic anhydride and pyridine gave 1-acetyl derivatives respectively in good yields.

1-Acetyl derivative of $IIId_1$: mp 135—136°C.

Found: C, 78.09; H, 7.86; N, 8.73%. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08%.

1-Acetyl derivative of $IIId_2$: mp 175—175.5°C.

Found: C, 78.12; H, 8.10; N, 9.27%. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08%.