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CONFORMATIONAL CHANGES IN DIACYL-TETRAHYDROPYRIDAZINE AND PIPERIDAZINE SYSTEMS

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Abstract—Conformational changes in both diacyltetrahydropyridazines and piperidazines have been studied by the NMR method. Processes involving both ring inversion and hindered rotation about the N—COR bonds have been recognized. The energy barriers to ring inversion are unusually high for six membered ring systems and appear to be associated with interaction between the adjacent N-acyl substituents.

THE temperature dependence of the NMR spectra of two tetrahydropyridazines (I and II) has recently been described[1] and the observed effects attributed to an unusually high energy barrier to conformational inversion of the six-membered ring[2] and hindered rotation about the N—CO_2R bonds. In this paper we report the results of an independent study of similar effects in a series of tetrahydropyridazine and piperidazine derivatives (III to XII), the results of this work are summarized in Table 1.

The results in Table 1 were generally obtained by standard methods of analysis[5,6] of the line shapes of coalescing systems in the NMR spectra of the compounds recorded at various temperatures. The rates of conformational change of VIII at 0° and IX at 20° were recorded by direct observation of the rates of attainment of conformational equilibrium in a solution of the crystalline compound (a single conformation) prepared at low temperature (−40°) (see Experimental). The assignments of spectral change to conformational change are based upon the discussion presented in this paper. With two exceptions the energy barriers quoted are based only upon coalescence temperatures or single temperature observations and the discussion presented in this paper is largely concerned with identifying the conformational changes involved since in some cases the free energy barriers to these changes are unusually large.

Conformational changes in tetrahydropyridazine derivatives

This investigation was initiated by the observation that the C(3) and C(6) methylene protons of III give rise to a broadened AB system in the NMR spectrum recorded at 35° (the normal probe temperature of the Varian A60 NMR Spectrometer used for

[1] J. C. Breliere and J. M. Lehn, *Chem. Comm.* 426 (1965).

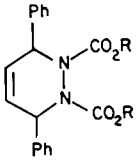
[2] Typical energy barriers to conformational inversion of six membered rings range from that for cyclohexane[3] [$\Delta F^{\ddagger} = 10{\cdot}5$ kcal/mole (−67°), $\Delta H^{\ddagger} = 10{\cdot}5$ kcal/mole, $\Delta S^{\ddagger} = 0$ e.u.] to the rather larger value measured for 3,3,6,6-tetramethyldioxan[4] [$\Delta F^{\ddagger} = 14{\cdot}6$ kcal/mole (12°), $\Delta H^{\ddagger} = 17{\cdot}9$ kcal/mole, $\Delta S^{\ddagger} = 14{\cdot}6$ e.u.]. Data for many other ring systems are quoted in Ref. 6.

[3] F. A. Bovey, F. P. Hood, E. W. Anderson and R. L. Kornegay, *J. Chem. Phys.* **41**, 2041 (1964).

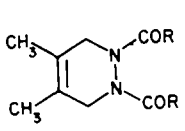
[4] G. Claeson, G. M. Androes and M. Calvin, *J. Amer. Chem. Soc.* **82**, 4428 (1961).

[5] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* Chap. 10. McGraw-Hill (1959).

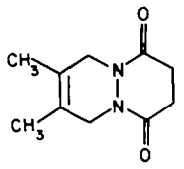
[6] L. W. Reeves, *Adv. Phys. Org. Chem.* **3**, 187 (1965).



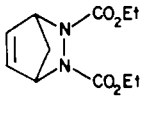
I R = CH_3
II R = Et



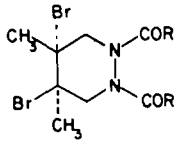
III R = OEt
VI R = CH_3
VII R = Ph



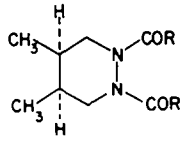
V



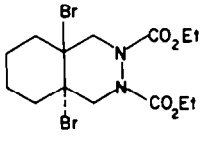
IV



VIII R = OEt
IX R = CH_3



X R = OEt
XI R = CH_3



XII

this work). This result suggested unusually high conformational rigidity of the ring system and when the NMR spectrum of III was recorded at a series of increasing temperatures it was found that the AB system coalesced to a broad singlet at 138° which became sharper at higher temperatures. By application of the appropriate formula[7] the rate of exchange of the A and B proton environments at the coalescence temperature was calculated, from this the free energy barrier to the exchange process could be obtained ($\Delta F^{\ddagger} = 20{\cdot}7$ kcal/mole at 138°). The observed spectral changes can only be attributed to hindered ring inversion since the C(3) and C(6) protons of all rapidly inverting ring systems would form an equivalent pair in each of the two methylene groups when examined by NMR spectroscopy (see XIII); but rotational isomerism about the N—CO_2R bonds could give rise to a maximum of four different A_2 systems. This result was unexpected[8] in view of the four trigonal atoms in the six-membered ring which would require only a small amount of angle deformation to reach even a planar transition state for the interconversion of half-chair conformations (XIII).

[7] R. J. Kurland, M. B. Rubin and W. B. Wise, *J. Chem. Phys.* **40**, 2426 (1964); M. Oki, H. Iwamura and N. Hayakawa, *Bull. Chem. Soc. Japan* **37**, 1685 (1964).

[8] Cyclohexene, with only two trigonal ring carbon atoms, has a very low barrier to ring inversion ($\Delta F^{\ddagger} = 5{\cdot}2$ kcal/mole at −164°, $\Delta H^{\ddagger} = 5{\cdot}3$ kcal/mole, $\Delta S^{\ddagger} = 1{\cdot}3$ e.u.), F. A. L. Anet and M. Z. Haq, *J. Amer. Chem. Soc.* **87**, 3147 (1965).

TABLE 1. ENERGY BARRIERS TO CONFORMATIONAL CHANGE IN TETRAHYDROPYRIDAZINE AND PIPERIDAZINE DERIVATIVES

Compd	Changes in NMR spectrum	Change in conformation	Energy barrier $\Delta F^{\ddagger}$, kcal/mole (°C)
I	Coalescence of C(4) and C(5) proton signals	Ring inversion[1]	18·9 (97°)
	Coalescence of low temp CO_2Me signals	Rotation about N—CO_2Me bond[1]	14·8 (−3°)
III	C(3) and C(6) proton signals change from AB to A_2 system	Ring inversion	20·7 (138°)
	Coalescence of low temp CO_2Et signals	Rotation about N—CO_2Et bond	14·7 (−7.5°)
IV	Coalescence of C(3) and C(6) proton signals	Rotation about N—CO_2Et bond	13·9 (−2°) (E_a = 15·4 kcal/mole $\log_{10} A$ = 14·0[d])
V	C(3) and C(6) proton signals remain as singlet	Ring inversion	<10·4 (−60°)[a]
VI	C(3) and C(6) proton signals stay as AB system	Ring inversion	>21·4 (160°)[b]
VII	C(3) and C(6) proton signals change from AB + A_2 to A_2 system	Rotation about N—COPh bond	14·9 (8°) (E_a = 15·0 kcal/mole $\log_{10} A$ = 12·9[d])
	Coalescence of low temp C(4) and C(5) Me signals	Ring inversion	
VIII	C(3) and C(6) proton signals change from AB + A′B′ system to AB system		20·1 (102·5°)
	Coalescence of low temp CO_2Et signals	Rotational about N—CO_2Et bond	19·8 (81°)
	Direct observation of equilibration		19·5 (0°)
IX	Direct observation of equilibration	Rotation about N—$COCH_3$ bond	21·9 (20°)
X	C(3) and C(6) proton signals change from multiplets to a single doublet	Ring inversion?	*ca.* 20 (120°)[c]
XII	C(3) and C(6) proton signals change from AB + A′B′ system to AB system	Rotation about N—CO_2Et bond	20·9 (116°)
	Coalescence of low temp CO_2Et signals		20·4 (90°)

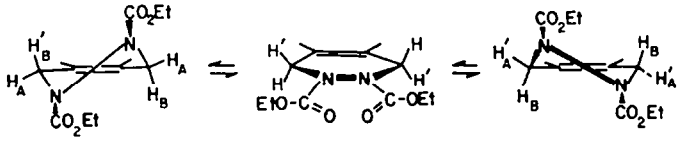
[a] The C(3) and C(6) proton signals are seen as a sharp singlet even at −60°, the maximum value of the free energy barrier quoted is based upon the values J_{AB} = 15·5 c/s, $\nu_0\delta_{AB}$ = 30 c/s (as for III).

[b] The AB system from the C(3) and C(6) protons shows little sign of broadening even at 160°, the actual height of the energy barrier is probably considerably higher than the minimum quoted.

[c] The observed coalescence of the C(3) and C(6) protons is complex (see Table 2) and the calculation is approximate.

[d] Rate constants and therefore A are in sec^{-1} units.

A similar high energy barrier to ring inversion has been reported[1] for I and II and the high energy of the transition state attributed to non-bonded interactions between the —CO_2R groups when the substituents on the two nitrogen atoms are



XIII[9]

coplanar (XIII). The approach of the two oxygen atoms[10] in a planar conformation (XIII) is 1·49 Å, but this interaction can obviously be relieved (at the expense of conjugation energy) by rotation about the N—CO_2Et bonds and by angle deformation. The planar diacyl hydrazine system of the transition state would presumably be electronically stable since N,N′-diformylhydrazine has a completely planar structure in the crystalline state.[11] It has however been suggested that the hydrazine molecule in solution is twisted so that the nitrogen lone pairs are mutually perpendicular[12] and similar lone pair interactions have recently been considered[13] in both substituted hydrazines and hydroxylamines. The significant non-planarity of formamide in the gaseous state[14] shows that considerable non-planarity of the substituents attached to nitrogen in amides is permissible with little increase in strain energy, although X-ray analysis of crystalline amides[15] is consistent with a planar arrangement of the substituents on nitrogen. The arguments used in this paper are based upon the assumption of trigonal stereochemistry at the nitrogen atoms of amide groups with the possibility of deformation towards a pyramidal configuration with little increase in energy.

If the above explanation of the high energy barrier to conformational inversion of tetrahydropyridazines (I, II and III) is correct, systems in which the non-bonded interactions between the acyl substituents in the transition state (XIIIa) are replaced by a bonded system should have a very much lower energy barrier to ring inversion. The succinoyl derivative (V) was prepared as an example of such a system, and the C(3) and C(6) methylene protons of V were observed as a sharp singlet in the NMR spectrum even at −60° and, assuming that this does not merely result from accidental magnetic equivalence of the two methylene protons in a frozen conformation, the energy barrier to the conformational inversion of V must be less than 10·4 kcal/mole at −60°.

The non-bonded interactions in the transition state may be dependent upon the resistance to rotation of the N—COR system. Whereas the diacetyl compound (VI) is extremely resistant to conformational inversion ($\Delta F^{\ddagger} > 21{\cdot}4$ kcal/mole at 160°) and the methylene protons appear as an AB system at all temperatures up to 160°, the

[9] In this and in similar diagrams throughout this paper H and H′ are used to label the individual hydrogen atoms, the subscripts A and B refer to the magnetic environment of the protons and are related directly to the observed NMR spectra.

[10] This distance is based upon N—C—O and N—N—C angles of 120° and bond lengths as follows: C=O, 1·23 Å; N—C, 1·32 Å; N—N, 1·40 Å.

[11] Y. Tomiie, C. H. Koo and I. Nitta, *Acta Cryst.* **11**, 774 (1958).

[12] W. G. Penney and G. B. B. M. Sutherland, *Trans. Farad. Soc.* **30**, 898 (1934).

[13] D. L. Griffith and J. D. Roberts, *J. Amer. Chem. Soc.* **87**, 4089 (1965).

[14] C. C. Costain and J. M. Dowling, *J. Chem. Phys.* **32**, 158 (1960).

[15] *Tables of Interatomic Distances and Configuration in Molecules and Ions* (Edited by L. E. Sutton). The Chemical Society, London (1965).

six-membered ring of the dibenzoyl derivative (VII) inverts much more readily ($\Delta F^{\ddagger} =$ 14·9 kcal/mole at 8°) and the low temperature AB system coalesces to a singlet at *ca.* 20°. The low temperature NMR spectrum of VII however is complex (Fig. 2 and Tables 1 and 2) and indicates that processes additional to ring inversion are involved (*vide infra*).

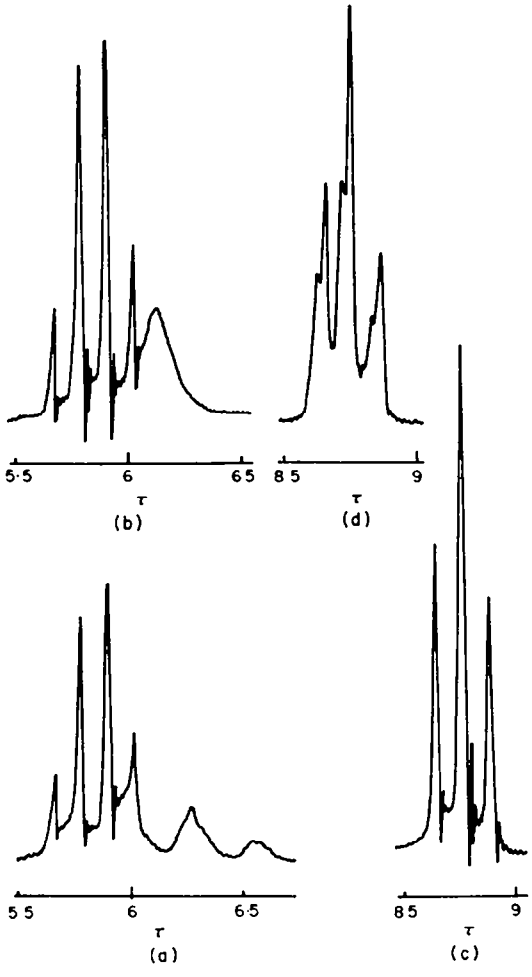


FIG. 1. NMR Spectrum of 1,2-dicarbethoxy-4,5-dimethyl-1,2,3,6-tetrahydropyridazine (III). (a and b) C(3) and C(6) protons and CH_3 of CO_2Et at 35° and 160°. (c and d) CH_3 of CO_2Et at 35° and −20°.

In addition to hindered ring inversion the low temperature NMR spectrum of III indicates conformational isomerism involving the N—CO_2Et groups. Thus the single triplet methyl resonance of the —CO_2Et group separates into two triplets (Fig. 1, Table 2) below −3°. The relative intensities of the triplets are approximately 2:1 and they therefore represent non-equivalent conformations of slightly different energies, but it is not possible to deduce which of the three possible arrangements of the two ester groups they represent. The remainder of the spectrum, apart from considerable

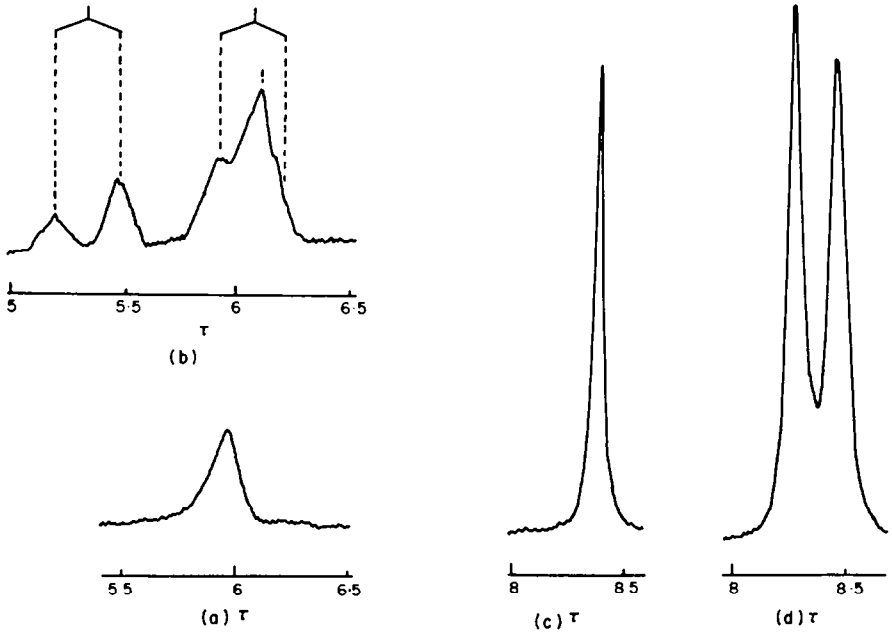
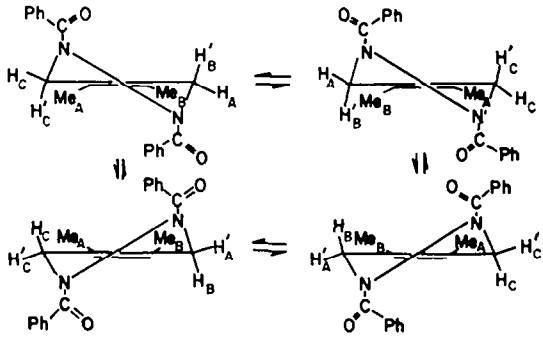


FIG. 2. NMR Spectrum of 1,2-dibenzoyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine (VII). (a and b) C(3) and C(6) protons at 40° and −15°. (c and d) C(4) and C(5) methyl groups at 35° and −17°.

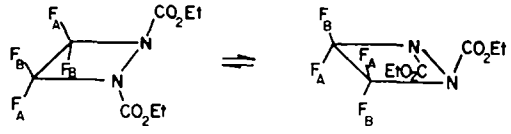
line broadening, is unchanged at low temperatures. The calculated energy barrier to rotation about the N—CO_2Et bonds ($\Delta F^{\ddagger}$ = 14·7 kcal/mole at −7·5°) is similar to that reported[1] for hindered rotation about the N—CO_2Me bonds of I ($\Delta F^{\ddagger}$ = 14·8 kcal/mole at −3°).

The temperature dependence of the NMR spectrum of VII appears to involve both ring inversion and rotational isomerism of the N—COPh groups. At low temperatures (Fig. 2 and Table 2) the C(3) and C(6) proton resonances are observed as a broadened AB system (2 protons) and a broad singlet (2 protons) which is superimposed on the B proton doublet, and the C(4) and C(5) methyl groups appear as two singlets (3 protons each). At higher temperatures the methylene proton signals coalesce to a broad singlet (4 protons) at the average chemical shift of the low temperature signals, at the same time the methyl groups coalesce to a singlet. The simplest conformational changes that would explain these observations are illustrated in XIV, ring inversion must be involved in addition to rotational changes of the N—COPh groups to account for the averaging of the methylene proton signals to a singlet in addition to coalescence of the two methyl resonances.

In order to separate ring inversion and rotational isomerism of the diacylhydrazine residue the bridged tetrahydropyridazine (IV) was prepared. The C(3) and C(6) protons, observed in the NMR spectrum as two singlets (broadened by coupling to the C(4) C(5) and C(7) protons) at low temperatures, coalesce to a single resonance at −2° which is resolved as a quintet (all *apparent* coupling constants equal) at 40° ($\Delta F^{\ddagger}$ = 13·9 kcal/mole at −2°, E_a = 15·4 kcal/mole, $\log_{10} A$ = 14·0). This result can be explained in terms of hindered rotational changes about the N—CO_2Et



bonds, but the actual conformation adopted by the diacylhydrazine system of IV is uncertain. Presumably the stereochemistry at the two nitrogen atoms approaches the pyramidal configuration[14] to avoid the non-bonded interactions that are present in the transition state for ring inversion of the mobile tetrahydropyridazine systems previously discussed. In fact the observed barrier to rotation is of the same order as that observed for I and III showing that the ground state conformation is not significantly destabilised by interaction between the two —CO_2Et substituents. Temperature dependent changes in the F^{19} resonance spectrum of the tetrafluoro compound (XV) have been attributed[16] to conformational isomerism of the type shown (at low temperature F^{19} seen as approx. AB system, singlet at high temperatures, $E_a = 8{\cdot}0$ kcal/mole. $\log_{10} A = 10$). These observations are also compatible with the inter-



XV

conversion of two non-planar cyclobutane conformations, with trigonal nitrogen atoms, which is hindered by the passage of one —CO_2Et group past the other. A conformational change analogous to XV would account for the observed changes in the NMR spectrum of IV

Conformational changes in piperidazine derivatives

The observation and explanation of the high energy barriers to ring inversion of diacyltetrahydropyridazines suggested that similar results would be found for piperidazines. Catalytic hydrogenation of III and VI gives the corresponding *cis*-4,5-dihydroderivatives (X) and (XI). The NMR spectrum of XI at 35° in both $CDCl_3$ and pyridine can be analysed in terms of two different ABX systems resulting from the ring protons (Fig. 3) with coupling constants J_{AX}, J_{BX}, $J_{A'X'}$ and $J_{B'X'}$ compatible with the dihedral angles[17] of a chair conformation (XVI); at the same time two distinct types of ring methyl group and acetyl methyl group are observed. These observations may be explained in terms of a rigid chair conformation (XVI), but

[16] W. D. Phillips, *Determination of Organic Structures by Physical Methods* Vol. 2 (Edited by F. C. Nachod and W. D. Phillips) p. 452. Academic Press (1962).

[17] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); *J. Amer. Chem. Soc.* **85**, 2870 (1963).

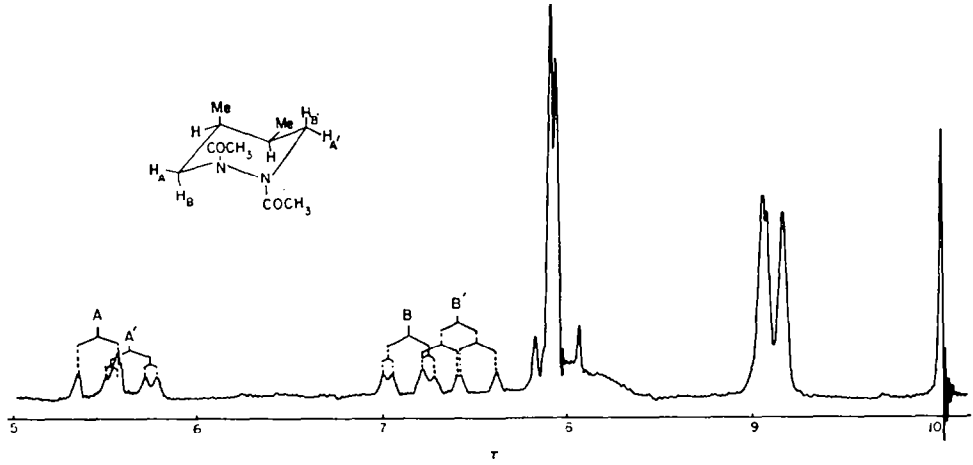
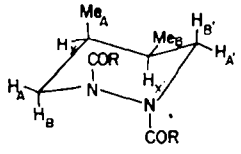
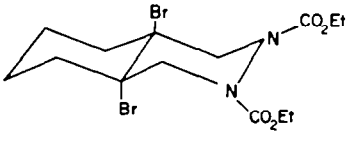


FIG. 3. NMR spectrum of 1,2-diacetyl-4,5-dimethyl-piperidazine at 35° in $CDCl_3$.

additional low intensity acetyl methyl signals suggest that other types of conformation (e.g. involving rotational isomerism of the N—$COCH_3$ groups) are present in low concentration at equilibrium. The spectrum of the dicarbethoxy compound (X) is less easy to analyse since the CH_2 protons of the —CO_2Et groups obscure the low field C(3) and C(6) proton resonances. However, the spectrum of X at high temperatures indicates rapid conformational inversion of the two chair forms and all four C(3) and C(6) protons are seen as a single doublet with no distinction between the protons *cis* and *trans* to the ring methyl groups. This result is interpreted as indicating rapid



XVI



XVII

inversion of a chair conformation with identical average environments for the exchanging protons A and B', and B and A' (see XVI).

The dibromo derivatives (VIII and IX) were expected to give rather simpler NMR spectra than the dihydro- derivatives, in which the C(3) and C(6) proton signals are complicated by additional coupling. The NMR spectrum of the ring methylene groups of VIII (Fig. 4 and Table 2) shows two different AB systems of slightly different intensity at 35°; these could represent either the two possible chair conformations (XVIII and XIX) (XVIII being the predominant conformer) or conformations differing by rotational isomerism about the N–CO_2Et bonds. The energy barriers to interconversion of the conformations suggested the former explanation ($\Delta F^{\ddagger} = 20{\cdot}1$ kcal/mole at 102·5°, 19·8 kcal/mole at 81° and 19·5 kcal/mole at 0°); these figures are based upon the coalescence of the two AB systems at 102·5° and the coalescence of the two low temperature—CO_2Et methyl triplets at 81°. The third value for the energy barrier is obtained by direct measurement of the rate of attainment of equilibrium

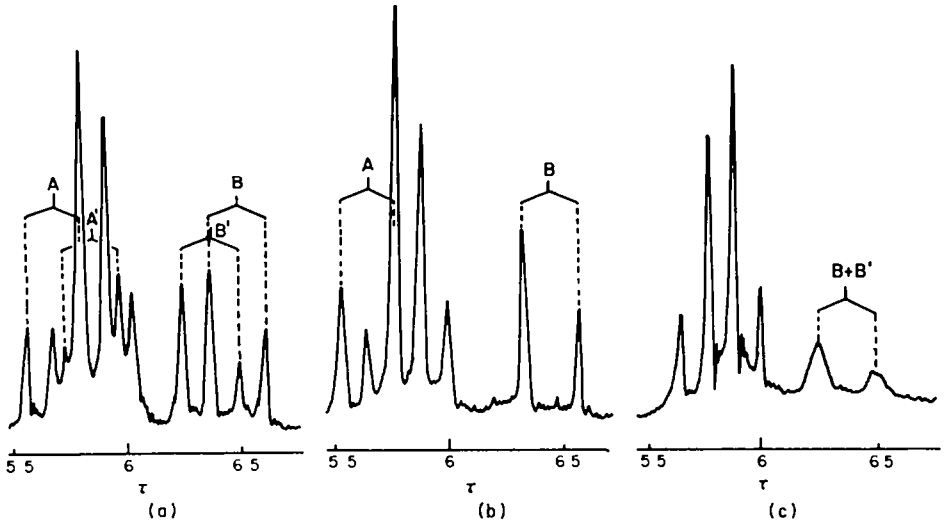


FIG. 4. NMR spectrum of 4,5-dibromo-1,2-dicarbethoxy-4,5-dimethylpiperidazine (VIII). C(3) and C(6) protons and CH_3 of CO_2Et (a) at 35°, (b) at −40° (freshly prepared solution) and (c) at 140°.

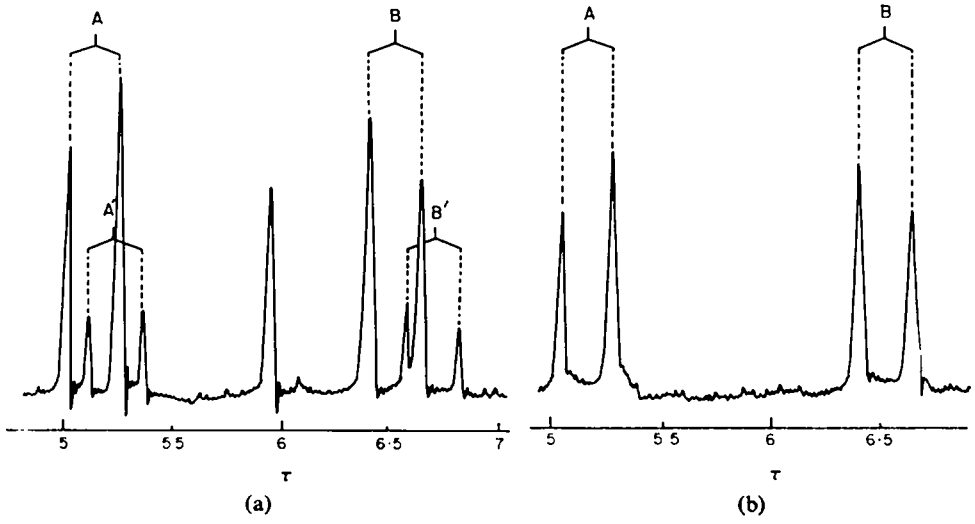
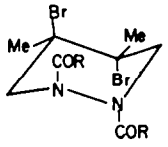


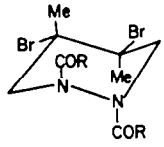
FIG. 5. NMR spectrum of 4,5-dibromo-1,2-diacetyl-4,5-dimethylpiperidazine (IX). C(3) and C(6) protons (a) at 35°, (b) at −20° (freshly prepared solution).

when a solution of the more abundant conformer (prepared by dissolving the crystalline compound in $CDCl_3$ at −40°) is maintained at 0° and the integrated AB and A′B′ signals from the ring methylene protons recorded after measured time intervals. However the *trans*-dibromide (XII), prepared by the addition of bromine to the Diels–Alder adduct of 1,2-dimethylenecyclohexane and ethyl azo-dicarboxylate, shows similar temperature dependence of the NMR spectrum of the methylene protons and the ester methyl groups (Tables 1 and 2). In this case the results can be interpreted as the consequences of hindered rotation about the N—CO_2Et bonds in the rigid *trans*-decalin-like conformation (XVII), and it is assumed by analogy that

similar hindered rotation of the N—CO_2Et groups in the chair conformation (XVIII, R = OEt) occurs for the dibromide (VIII). Whether ring inversion of XVIII is rapid or whether the alternative chair conformation (XIX) is in too low concentration to be observable in the NMR spectrum is not known. The rapid inversion of the chair ring would be unexpected in view of the apparent rigidity of the tetrahydropyridazines since the arguments used to account for the rigidity of this system would also apply to the hexahydro systems. Further work with the piperidazines is required to clarify this point.



XVIII



XIX

The rates of similar conformational changes in the diacetyl-dibromopiperidazine (IX) are too slow to measure by the NMR method, and, using integrated spectra, the rate of transformation of the crystalline (most stable conformation) into the equilibrium mixture of at least two conformations was observed directly. The initial conformation is one in which the C(3) and C(6) protons are observed as a single AB system which, at 20°, slowly comes into equilibrium with a less stable conformation giving a second AB system and a singlet A_2 system.* These changes by analogy with the other dibromides are assumed to involve rotational isomerism about the N—$COCH_3$ bonds in a chair conformation (XVIII, R = CH_3).

The higher energy barrier to rotation about the N—CO_2Et bond in XII and VIII as compared with the tetrahydro compounds (III and IV) is surprising, and since these barriers are comparable in size with those postulated for ring inversion in the tetrahydro compounds it is not possible in these systems to characterize the type of conformational change occurring by the size of the energy barrier involved. The evidence for an abnormally high energy barrier to ring inversion in the piperidazines (X and XI) is not fully convincing but it is hoped that further study of the NMR spectra of suitable diacylpiperidazines will provide more compelling evidence for the rates of ring inversion in these compounds. The possibility of conformations other than the chair conformation,[18] and the half-chair conformation for the tetrahydropyridazines, also requires further consideration. Previous NMR studies[19] of *trans*-3,4-dihydroxypiperidazine derivatives led to the conclusion that these compounds adopted the conformation with all substituents axial on a chair ring.

Conformational changes in acylic hydrazine derivatives

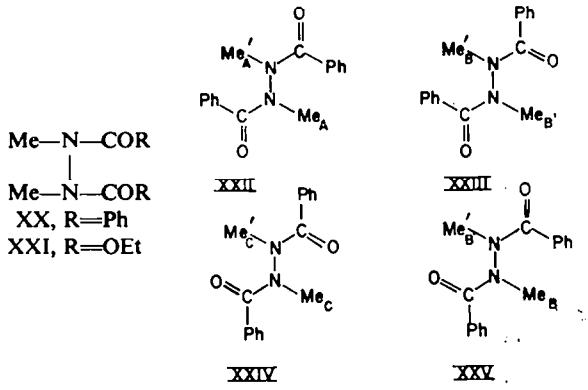
The diacyl hydrazines (XX and XXI) represent systems in which only rotational isomerism about the N—COR bonds in a planar system is expected. Three *trans*-coplanar conformations of XX are possible (presumably the more stable arrangement about the N—N bond[13]) resulting in the possibility of up to four different N—CH_3

* Alternative explanations are possible since there is a maximum of three rotational isomers, and also the possibility of chair–boat equilibria.

[18] A. Mc L. Mathieson, *Tetrahedron Letters* 81 (1963).

[19] W. Koch and H. Zollinger, *Helv. Chim. Acta* **46**, 2697 (1963).

signals for slow rotational isomerism (XXII to XXV) and rapid equilibration would simplify the spectrum to a single N—CH_3 signal. The NMR spectrum of the dibenzoyl-



dimethylhydrazine (XXI) shows two N—CH_3 signals at low temperatures with the intensity ratio 5:4 which coalesce to a single signal at 17° ($\Delta F^{\ddagger} = 14{\cdot}9$ kcal/mole at 17°), at the same time the low temperature C_6H_5 multiplet coalesces to a broad singlet. If the assumption is made that Me_A and Me_B, and Me_C and Me'_B, represent the two types of methyl group observable at low temperature then the changes observed in the NMR spectrum can be explained by equilibrium between two or all three of the possible *trans*-coplanar configurations.

Similar arguments apply to the dicarbethoxydimethylhydrazine (XXI), but in this case the low temperature NMR spectrum shows only one type of N-Me group and two triplets (intensity ratio 2:1) from the —CO_2Et methyl groups which coalesce to a single triplet at 22°C ($\Delta F^{\ddagger} = 16{\cdot}2$ kcal/mole). These observations are again compatible with equilibrium between two or all three of the possible *trans*-coplanar conformations involving rotation about the N—CO_2Et bonds.

The free energy barriers to rotation about the N—COPH and N—CO_2Et bonds in the simple hydrazine derivatives (XIX and XX) are similar to those determined for this type of conformational change in the more complex cyclic hydrazine derivatives (VII, III and IV). The simpler case of rotation about the CO—N bonds of amides has been studied by several groups and the free energy barrier to rotation about the CO—N bond of N,N-dimethylbenzamide[20] ($\Delta F^{\ddagger}$ 15·3 kcal/mole at 25·2°) is similar to that observed for the hydrazine derivatives. However, in the case of the amide the energy barrier is both an enthalpy and entropy barrier ($E_a = 7{\cdot}7 \pm 0{\cdot}5$ kcals/mole, $\log_{10} A = 7{\cdot}2 \pm 1{\cdot}4$) and a more detailed examination of temperature effects on the NMR spectra of acyl hydrazines is being undertaken to obtain enthalpies and entropies of activation for conformational isomerism.

EXPERIMENTAL

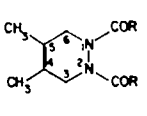
All NMR spectra were measured using a Varian A60 spectrometer with variable temp probe; temps were measured using MeOH and ethylene glycol standards and are accurate to ±2°. Rates of conformational interconversion k_c at the coalescence temp were obtained using the formula[7]

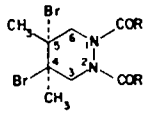
$$k_c = \pi(\nu_0\delta_{AB}^2 + 6J_{AB}^2)^{1/2}/\sqrt{2}$$

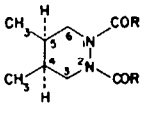
where $\nu_0\delta_{AB}$ is the low temp separation of the coalescing proton resonances in c/s (calculated in the usual way for AB systems) and does not vary to any great extent with temp in any of the systems

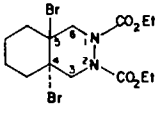
[20] M. T. Rogers and J. C. Woodbury, *J. Phys. Chem.* **66**, 540 (1962).

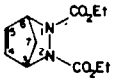
TABLE 2. NMR SPECTRA OF TETRAHYDRO- and HEXAHYDRO-PYRIDAZINE DERIVATIVES


A


B


C


XII


IV

	Compound	Solvent	°C	C(3) and C(6) H	Substituents on N(1), N(2)	C(4), C(5) Me groups	Others
	III	PCE	150°	6·14 (broad s) [4]	8·78 (t) [6], 5·85 (q) [4]	8·47 (s) [6]	
A	R = OEt	PCE	35°	5·91 (broad d) [2], 6·39 (broad d) [2] J = 15·5	8·74 (t) [6], 5·85 (q) [4]	8·35 (s) [6]	
		CCl_4	−20°		8·74 (t), 8·70 (t) [6], 5·85 (q) [4]	8·33 (s) [6]	
	VI	$CDCl_3$	35°	5·29 (broad d) [2], 6·57 (broad d) [2] J = 15·5	7·91 (s) [6]	8·35 (s) [6]	
A	$R = CH_3$						
	VII	$CDCl_3$	35°	5·98 (broad s) [4]	2·68 (s) [10]	8·42 (s) [6]	
		$CDCl_3$	−17°	5·37 (broad d) [1], 6·04 (broad d) [1] J = 16·5		8·30 (s) [3]	
A	R = Ph			6·12 (broad s) [2]	2·2–3·0 (m) [10]	8·48 (s) [3]	
	V	$CDCl_3$	35°	5·89 (s) [4]	7·35 (s) [4]	8·29 (s) [6]	
A	$R = (CH_2)_3$	$CDCl_3$	−50°	5·81 (s) [4]	7·25 (s) [4]	8·25 (s) [6]	
	VIII	PCE	100°	5·72 (broad d) [2], 6·35 (broad d) [2] J = 15	8·75 (t) [6], 5·80 (q) [4]	8·07 (s) [6]	
		PCE	50°	5·67 (d) [1·06], 6·43 (d) [1·06] J = 15; 5·85 (d) [0·94], 6·27 (d) [0·94] J = 14·5	8·75 (t), 8·70 (t) [6], 5·80 (q) [4]	8·07 (s) [6]	
B	R = OEt						
		$CDCl_3$	−20*	5·67 (d) [2], 6·43 (d) [2] J = 15	8·80 (t) [6], 5·80 (q) [4]	8·08 (s) [6]	
	IX	$CDCl_3$	20†	5·16 (d) [1·4], 6·51 (d) [1·4] J = 14; 5·26 (d) [0·3], 6·69 (d) [0·3] J = 14; 5·93 (s) [0·6]	7·85 (s), 7·67 (s) [6]	7·98 (s), 7·95 (s) [6]	
B	$R = CH_3$						

		$CDCl_3$	20°*	5·16 (d) [2] 6·51 (d) [2] } J = 14	7·85 (s) [6]	7·98 (s) [6]	
	X	CCl_4	35°	5·6–6·3 (m) [2] 6·8–7·5 (m) [2]	8·76 (t) [6], 5·89 (q) [4]	9·12 (d, J = 7) [6]	C(4) and C(5) H 7·8–8·5 (m) [2]
C	R = OEt	Neat	200°	6·57 (d,J = 4·5) 4	8·77 (t) [6], 5·88 (q) [4]	9·10 (d, J = 6·5) [6]	8·13 (approx. sextet) [2]
	XI	$CDCl_3$	35°	5·47 [1] 7·13 [1] } AM of AMX J_{AM} = 13·0, J_{AX} = 1·3, J_{MX} = 2·9 5·66 [1] 7·41 [1] } A′M′ of A′M′X′ $J_{A'M'}$ = 12·6, $J_{A'X'}$ = 3·6, $J_{M'X'}$ = 11·4	7·92 (s) [approx. 6]		C(4) and C(5) H
					7·82 (s) 8·07 (s) } [low intensity]	9·11 (d, J = 6·5) [6]	7·7–8·4 (m) [2]
		Pyridine	35°	5·45 [1] 7·17 [1] } AM of AMX J_{AM} = 13·0, J_{AX} = 1·4, J_{MX} = 2·8 5·62 [1] 7·43 [1] } A′M′ of A′M′X′ $J_{A'M'}$ = 12·6, $J_{A'X'}$ = 4·1, $J_{M'X'}$ = 11·6	7·91 (s) [approx. 3] 7·95 (s) [approx. 3]	9·19 (d, J = 6·5) [3]	C(4) and C(5) H
C	$R = CH_3$				7·86 (s) 8·02 (s) } [low intensity]	9·32 (d, J = 6·5) [3]	8·0–8·6 (m) [2]
	XII	PCE	150°	5·79 (d) [2] 6·30 (d) [2] } J = 14·5	8·76 (t) [6], 5·87 (q) [4]		C(4) and C(5)$(CH_3)_4$ 7·6–8·4 (m) [8]
		PCE	35°	5·66 (d) [1·2] 6·35 (d) [1·2] } J = 14·5 5·87 (d) [0·8] 6·17 (d) [0·8] } J = 14·5	8·76 (t) 8·73 (t) } [6], 5·82 (q) [4]		7·6–8·4 (m) [8]
	IV	CCl_4	60°	4·93 (qu, J = 1·7) [2]	8·77 (t) [6], 5·87 (q) [4]		C(4) and C(5) H 3·52 (t, J = 1·7) [2] C(7) H 8·33 (broad s) [2]
		CCl_4	−21°	4·73 (broad s) [1] 5·07 (broad s) [1]	8·72 (t) [6], 5·83 (q) [4]		C(4) and C(5) H 3·45 (unresolved) [2] C(7) H 8·30 (broad s) [2]

s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = unresolved multiplet. The figures in brackets [ ] refer to the integrated proton count. PCE refers to pentachloroethane.

* Spectrum of a solution prepared at −40°.

† Spectrum recorded after 1 hr at 20°.

examined. The value of $\Delta F^{\ddagger}$ was then calculated using the Eyring equation. E_a and $\log_{10} A$ were obtained in the usual way by plotting $1/T$ against $\log_{10} k$, the exchange rate k at the temp T was calculated below the coalescence temp by the method of Gutowsky and Holm[21] and above the coalescence temp by using the equation[5,22] $k = \pi v_0 \delta_{AB}^2/2(W - W_0)$ where W is the observed line width at half height in c/s and W_0 is the line width in the absence of exchange broadening.

Compounds III,[23,24] IV,[25] VII,[23] VIII,[24] X,[24] XX[26] were prepared by established methods and had NMR spectra (Table 2) in accord with their structures.

1,2-*Diacetyl*-4,5-*dimethyl*-1,2,3,6-*tetrahydropyridazine* (VI). 4,5-Dimethyl-1,2,3,6-tetrahydrapyridazine[23] was acetylated with excess AcCl–Ac_2O and the product recrystallized from ether to give the *diacetyl deriv.*, m.p. 106°. (Found: C, 60·99; H, 8·16; N, 14·26. $C_{10}H_{16}N_2O_2$ requires: C, 61·19; H, 8·22; N, 14·28%.) The *dibromide* (IX) prepared by the action of Br_2–CCl_4 was recrystallized from EtOH–ether as colourless needles, m.p. 154°. (Found: C, 33·86; H, 4·59; N, 7·52; Br, 45·23. $C_{10}H_{16}Br_2N_2O_2$ requires: C, 33·74; H, 4·53; N, 7·87; Br 44·89%.)

1,2-*Succinoyl*-4,5-*dimethyl*-1,2,3,6-*tetrahydropyridazine* (V). 4,5-Dimethyl-1,2,3,6-tetrahydropyridazine (0·56 g) and succinic anhydride (0·5 g) were heated at 160° for 5 hr under N_2. The product in ether was washed with $NaHCO_3$aq and evaporated to give the crude product which was recrystallized from ether–CCl_4 to give the *succinoyl deriv.*, m.p. 123° (0·42 g, 43%). (Found: C, 61·83; H, 7·19; N, 14·29. $C_{10}H_{14}N_2O_2$ requires: C, 61·84; H, 7·26; N, 14·43%.)

1,2-*Diacetyl*-4,5-*dimethylpiperidazine* (XI). Compound VI in EtOH was reduced with H_2 and Adams PtO_2 catalyst. The product was recrystallized from ether–light pet. to give the *diacetylpiperidazine* (90%), m.p. 67°. (Found: C, 60·98; H, 8·89; N, 14·48. $C_{10}H_{18}N_2O_2$ requires: C, 60·57; H, 9·15; N, 14·14%.)

2,3-*Dicarbethoxy*-9,10-*dibromodecahydrophthalazine* (XII). A solution of 1,2-dimethylenecyclohexane[27] (0·18 g) and diethyl azodicarboxylate (0·3 g) in ether (20 ml) was refluxed for 4 hr and allowed to stand overnight. The ether was removed by evaporation and the adduct purified by short path distillation at 0·05 mm (0·38 g, 81%). A solution of Br_2 (0·22 g) in CCl_4 (3 ml) was added to the adduct in CCl_4 keeping the temp of the solution below 10°. After 8 hr at room temp the solvent was evaporated and the residue crystallized from ether–light pet. to give the *dibromodecahydrophthalazine*, m.p. 100° (0·48 g, 80%). (Found: C, 37·84; H, 5·08; N, 6·49; Br, 36·18. $C_{14}H_{22}N_2O_4Br_2$ requires: C, 38·03; H, 5·02; N, 6·34; Br, 36·15%.)

N,N'-*Dimethyl*-N,N'-*dicarbethoxyhydrazine*. N,N'-Dimethylhydrazine hydrochloride[28] (5 g) was treated with ethyl chloroformate (5·6 g) in aqueous ethanolic Na_2CO_3. The product was purified by distillation to give the *dimethyldicarbethoxyhydrazine* b.p. 126°/15 mm (3·1 g, 60%). (Found: C, 46·95; H, 7·83; N, 13·89. $C_8H_{16}N_2O_4$ requires: C, 47·07; H, 7·90; N, 13·73%.)

Direct observation of isomerization rates for VIII *and* IX. The crystalline dibromohexahydropyridazine (single conformation) was dissolved in $CDCl_3$ at −40° and the spectrum recorded at measured time intervals at 0° (for VIII) and 20° (for IX). The rate of interconversion of the more stable stereoisomer of VIII into an equilibrium mixture of two conformations was readily obtained from the kinetics of the reversible equilibrium:[29]

$$\text{A (53\%)} \underset{k}{\overset{k'}{\rightleftharpoons}} \text{B (47\%)}$$

$$k = 1{\cdot}87 \times 10^{-3}\ \text{sec}^{-1} \text{ at } 0°$$

The rate of conversion of the more stable conformer of IX into an equilibrium mixture of two conformers A and B was obtained by considering the kinetics of the process:[29]

$$\text{A (70\%)} \underset{k}{\overset{k'}{\rightleftharpoons}} \text{B (30\%)}$$

$$k = 3{\cdot}75 \times 10^{-4}\ \text{sec}^{-1} \text{ at } 20°$$

[21] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.* **25**, 1228 (1956).
[22] F. A. L. Anet, *J. Amer. Chem. Soc.* **86**, 458 (1964).
[23] P. Baranger and J. Levisalles, *Bull. Soc. Chim. France* 704 (1957).
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[25] J. C. J. McKenzie, A. Rodgman and G. F. Wright, *J. Org. Chem.* **17**, 1666 (1952).
[26] H. H. Hatt, *Org. Synth.* **16**, 18 (1936); *Coll. Vol. II*, p. 209.
[27] W. J. Bailey and H. R. Golden, *J. Amer. Chem. Soc.* **75**, 4780 (1953).
[28] The values in parentheses refer to the percentage composition of the equilibrium mixture.