Tetrahedron. Vol. 26, pp. 3369 to 3387. Pergamon Press 1970. Printed in Great Britain

PROTON MAGNETIC RESONANCE STUDIES OF COMPOUNDS WITH BRIDGEHEAD NITROGEN ATOMS—XIII[1]

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH METHYL SUBSTITUTED PERHYDRO-DIPYRIDO[1.2-*c*, 2′.1′-*f*]PYRIMIDINES

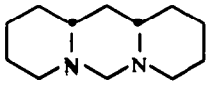
P. J. CHIVERS and T. A. CRABB

Chemistry Department, Portsmouth Polytechnic

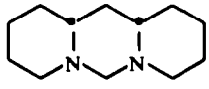
(*Received in the UK* 25 *February* 1970; *Accepted for publication* 24 *March* 1970)

Abstract—*Syn* and *anti* perhydrodipyrido[1.2-*c*, 2′,1′-*f*]pyrimidine and fourteen monomethyl substituted derivatives have been synthesized and their configurations and preferred conformations assigned on the basis of the 2800–2600 cm^{-1} region of their IR spectra and from a study of the geminal coupling constant and difference in chemical shift between the C6 methylene protons.

PERHYDRODIPYRIDO[1.2-*c*, 2′.1′-*f*]PYRIMIDINE formally resembles its carbocyclic analogue perhydroanthracene, but the presence of the bridgehead N atoms gives rise to important stereochemical differences between the two systems. The position of the conformationally mobile N atoms at the ring fusions makes it possible for a particular isomer of the heterocyclic system to exist as an equilibrium mixture of several conformations. In Figs 1 and 2 some of the possible conformations of *syn* (I) and *anti* (II) perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidine are shown and in each case these are interconvertible by N inversion and ring inversion. The replacement of two



I



II

C—H bonds by N lone pair electrons changes the number of non-bonding interactions and the presence of two hetero-atoms may allow significant dipole–dipole interactions to occur; both of these effects may influence the position of conformational equilibrium.

The relative stabilities of the perhydroanthracenes were established by equilibration[2] and epimerization studies[3] and by heats of combustion measurements[4] and the results explained in conformational terms.[5,6] Since the three most stable perhydroanthracenes are the *trans–syn–trans*, *cis–anti–trans**, and the *cis–anti–cis* isomers the preferred conformations for syn perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidine (I) and for the *anti* isomer (II) might be expected to be *trans–syn–trans* (Ia)

* In the case of the perhydroanthracenes the *cis–anti–trans* is also the *cis–syn–trans* isomer. In the perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidines the prefix *syn* or *anti* refers to the orientation of the angular CH bonds.

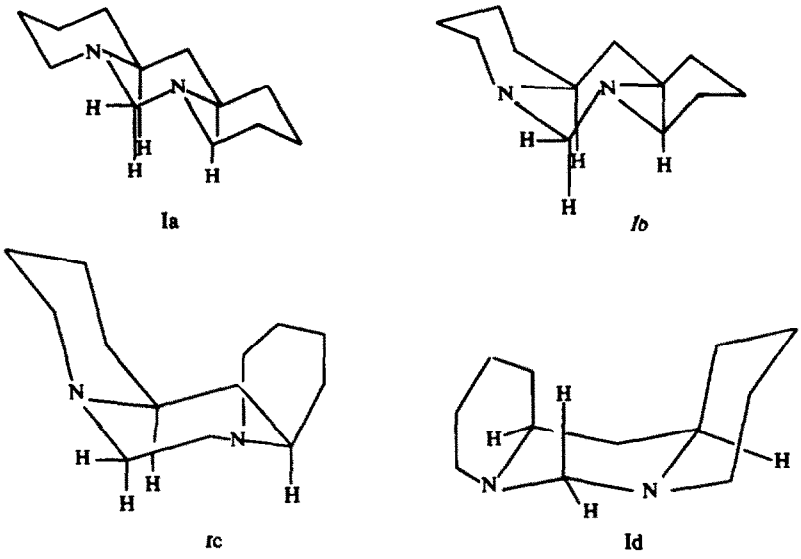


FIG 1. Possible conformations of *syn* perhydrodipyrido[1.2-*c*, 2'.1'-*f*]pyrimidine.

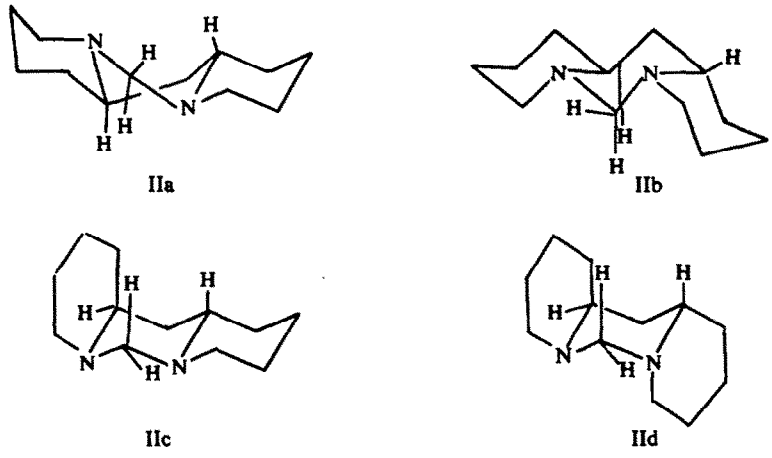


FIG 2. Possible conformations of *anti* perhydrodipyrido[1.2-*c*, 2'.1'-*f*]pyrimidine.

and *cis–syn–trans* (Ib) for I and *trans–anti–cis* (IIb = IIc) and *cis–anti–cis* (IId) for II. The two *cis–syn–cis* conformations Ic and Id are unstable because of *syn*-axial methylene interactions, but the *trans–anti–trans* conformation (IIa) with a skew boat central ring may not be as unstable as its carbocylic analogue (making comparisons within the same series) since the replacement of two CH bonds by nitrogen line pairs of electrons may have considerably reduced non-bonded interactions.

The importance of dipolar interactions in influencing conformation has long been

recognized and its effect on the conformations of bicyclic bridgehead N compounds possessing a 1,3-arrangement of heteroatoms discussed.[7,8] *Syn* axial lone pair interactions have also been discussed[9] in connection with hexahydropyrimidines. Since the presence of *syn* axial lone pairs of electrons destabilize a conformation this effect disfavours the *trans–syn–trans* (Ia), and the *trans–anti–cis* (IIb=IIc) conformations but increases the relative importance in particular of the *cis–syn–trans* conformation (Ib). It was in order to assess the relative importance of the factors capable of influencing the position of conformational equilibria of *syn* and *anti* perhydrodipyrido[1.2-*c*, 2'.1'-*f*]pyrimidines and to extend our knowledge of the NMR spectra of saturated heterocyclic systems that this work was undertaken.

Information regarding the predominant conformations of I and II should be readily obtainable from the Bohlmann (28000–2600 cm^{-1}) region of their IR spectra, and from a knowledge of the chemical shift difference (Δ)[11] and the geminal coupling constant (J_{gem}) between the C6 methylene protons since correlations have been established between these spectral parameters and the stereochemistry of related systems.[7, 8, 10]

In the case of the *syn* isomers, Ia is expected to show very strong Bohlmann bands since it possesses five CH bonds α to N anticoplanar with the N lone pair whereas Ib (three correctly orientated CH bonds) is expected to show much less intense absorption. Ic and Id should exhibit only very weak bands in the 2800–2600 cm^{-1} region. Similar arguments apply to the conformations of the *anti* isomers (Fig 2) and in this case IIa is also expected to show Bohlmann bands since these have been observed[12] in the IR spectra of some lupin alkaloids containing a boat ring. However, the presence of even substantial amounts of a *cis* fused conformation in equilibrium with a *trans* fused conformation cannot be ruled out solely from an IR study of the perhydrodipyrido[1.2-*c*, 2'.1'-*f*]pyrimidines.

A priori the J_{gem} of the C6 methylene protons should be ca − 8 Hz (negative sign assumed) for Ia, Id, and IIb (=IIc) since in these conformations both N lone pairs of electrons and a C6—H bond are anticoplanar. J_{gem} for Ib and IId should be ca. − 11·5 Hz (one N lone pair *anti* and the other skew to the CH bond) and for Ic ca. − 13·5 Hz (both N lone pairs skew to the C6 methylene bonds).[13] Δ (C6 methylene) should decrease along the series Ia, Ib, Ic for similar stereochemical reasons. A recent discussion (including all relevant references) of the factors contributing to the chemical shifts of protons α to N has been given by Lambert.[11]

Synthesis

The synthesis of the compounds discussed in this paper is summarised in Fig. 3. Several methods for the preparation of di-(2-pyridyl) methane have been described[14] and the route chosen for adaptation to the synthesis of Me substituted derivatives of I and II was that starting from the Me substituted 2-bromopyridines, since these are readily obtainable[15] from the commercially available amino-picolines.

The 2-pyridyl-2-(methylpyridyl)methanols were prepared from pyridine-2-aldehyde and the appropriate methyl pyridyl lithium. The methanols were converted to the 2-pyridyl-2-(methylpyridyl) chloromethanes by treatment with thionyl chloride in benzene and these were hydrogenolysed by zinc powder-glacial acetic acid to the 2-pyridyl-2-(methylpyridyl)methanes. The di(2-pyridyl)methanes in glacial acetic acid solution were hydrogenated over Adams catalyst to a mixture of diastereoisomeric

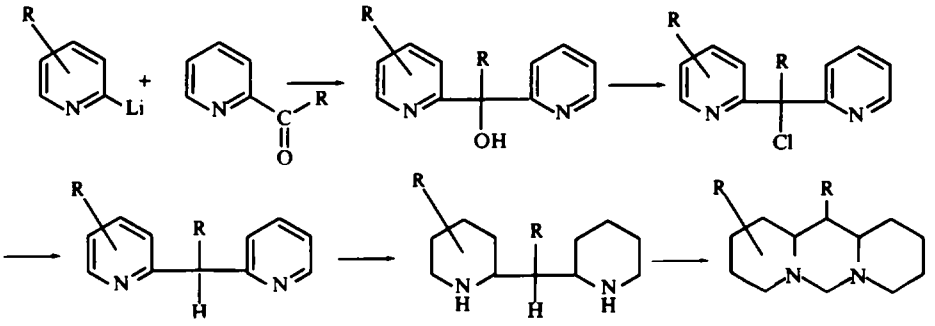


FIG 3. Synthesis of methyl substituted perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidine.

2-piperidyl(2-methylpiperidyl)methanes which were cyclized with formaldehyde to the required monomethylperhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidines. The 12-Me substituted compounds were obtained by the same route using acetyl pyridine in place of pyridine 2-aldehyde. The individual isomers were obtained by preparative gas chromatography or by column chromatography of the resultant mixtures of diastereoisomeric tricyclic compounds. The percentage of isomers obtained in each case is given in Table 1.

TABLE 1. PERCENTAGE ISOMERS OF THE MONOMETHYLPERHYDRODIPYRIDO[1.2-*c*, 2′.1′-*f*]PYRIMIDINES OBTAINED BY ROUTE SHOWN IN FIG 3

Perhydrodipyrido[1.2-*c*, 2′.1′-*f*] pyrimidines	% Isomers obtained			
	Syn		*Anti*	
	Axial Me	Equatorial Me	Axial Me	Equatorial Me
Unsubstituted compound	50		50	
1-Methyl	55(V)		30(XII)	15(XIII)
2-Methyl		50(VI)		50(XIV)
3-Methyl	35(VII)	15(VIII)	25(XV)	25(XVI)
4-Methyl		50(IX)		50(XVII)
12-Methyl	15(X)	35(XI)		50(XVIII)

RESULTS AND DISCUSSION

In order to present the results of the spectral studies on the methyl substituted perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidines as clearly as possible the data on which the assignment of configuration and of predominant conformation were made is given first and this is followed by a separate more detailed discussion on the position of equilibria in these compounds.

(a) *Assignment of configuration and of predominant conformations*

syn *and* anti *Perhydrodipyrido*[1.2-*c*, 2′.1′-f]*pyrimidine.* The two isomers of per-

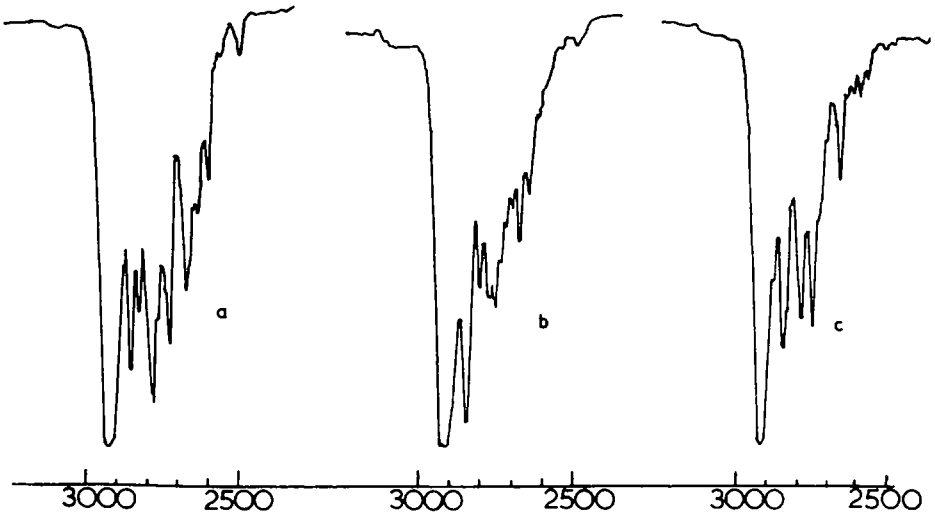
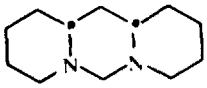
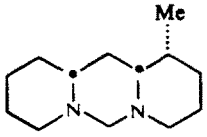
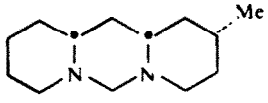
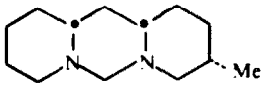
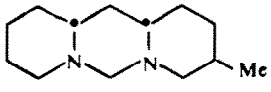
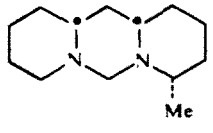
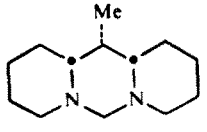
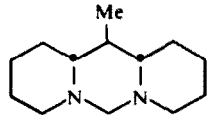


FIG 4. IR spectra (2800–2600 cm^{-1} region) of (a) *syn* and (b) *anti* perhydrodipyrido-[1.2-*c*, 2′.1′-*f*]pyrimidine and of (c) quinolizidine.

hydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidine were obtained as solids m.p. 81° and m.p. 52° by the route shown in Fig 3 (R=R=H). The isomer possessing the m.p. 81° showed more intense absorption in the 2800–2700 cm^{-1} region of the IR (Fig 4) than did the lower m.p. isomer, an observation consistent with the former isomer possessing the *trans syn trans* stereochemistry (Ia) (five α CH bonds anticoplanar with the N lone pair) and the latter the *trans anti cis* stereochemistry (IIb=IIc; three correctly orientated α CH bonds). In fact the IR absorption of the low m.p. isomer resembled that of quinolizidine (Fig 4) which also has three axial CH bonds α and *trans* to the N lone pair. The NMR evidence (Tables 2 and 3) was in accord with these assignments. The high m.p. isomer showed for the C6 methylene protons a J_{gem} of − 8·5 Hz and a Δ of 1·00 ppm, NMR parameters almost identical with those observed[8] for *cis* 4,6-3,4-dimethyl 1,3-diazabicyclo[4.4.0]decane (J_{gem} = − 8·8 Hz, Δ = 0·96 ppm) which has been assigned conformation III (predominant conformation at room temperature). Evidence for the absence of appreciable quantities of the *cis syn trans* conformation Ib in equilibrium with Ia at room temperature comes from a comparison of Ib with IV. Since both structures have one N lone pair skew and one *anti* to the axial CH proton between the nitrogen atoms a similar J_{gem} should be observed for both. IV shows[8] a J_{gem} of − 11·4 Hz and so the NMR spectrum of an equilibrium mixture of Ia and Ib would give a J_{gem} value for the C6 methylene protons less than − 8·5 Hz.

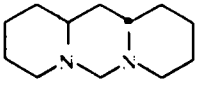
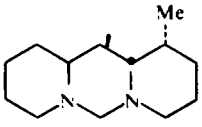
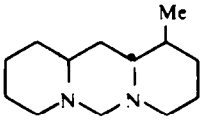
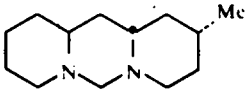
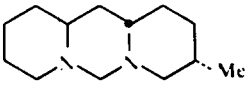
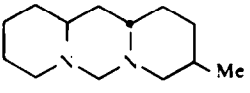
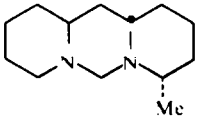
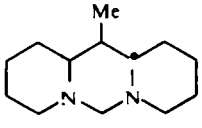
The close correspondence between the NMR parameters of this isomer of perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidine and III suggests similar structures for both compounds, cf. III and Ia. In addition there is a two proton broadened doublet (J ca. − 9 to − 10Hz) at 7·28 τ indicative[16] of two C—CH protons α and skew to N lone pairs. In Ia there are two such protons (H5eq and H8eq) in Ib there are three (H5eq, H8eq, and H11a.ax). This data together with the intense absorption in the IR shows the

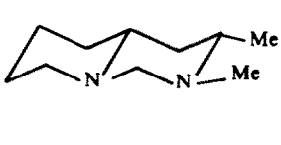
TABLE 2. NMR SPECTRA OF *syn* PERHYDRODIPYRIDO[1.2-*c*, 2′.1′-*f*]PYRIMIDINES

Co	Compound	No.	C6 Methylene Protons				Centre of Me doublet and "J_{CH-Me}"			
			$-J$ (Hz)	H6 eq (τ)	H6 ax (τ)	Δ	Equatorial		Axial	
		I	−8·5[a]	6·56	7·56	1·00				
		V	−9[a]	6·50	7·48	0·98			9·00	6·7
		VI	−8·5	6·52	7·56	1·04	9·10	4·0		
		VII	−8·8[a]	6·56	7·48	0·92			8·88	7·0
		VIII	−8·6[a]	6·50	7·56	1·06	9·16	5·5		
		IX	−8·5	6·15	7·75	1·60	8·94	5·8		
		X	−8·7	6·46	7·75	1·28			9·00	6·5
		XI	−8·8	6·55	7·47	0·92	9·15	4·0		

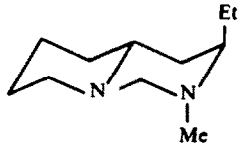
[a] Measured at 100 MHz. Δ Difference in chemical shift between H6eq and H6ax.

TABLE 3. NMR SPECTRA OF *anti* PERHYDRODIPYRIDO[1.2-*c*, 2′.1′-*f*]PYRIMIDINES

Compound	No.	C6 Methylene protons				Centre of Me doublet and "J_{CH-Me}"			
		$-J$ (Hz)	H6eq (τ)	H6ax (τ)	Δ	Equatorial		Axial	
	II			6·65					
	XII	9·5	6·30	6·76	0·46			9·05	6·0
	XIII			6·65		9·20	5·3		
	XIV			6·68		9·08	5·0		
	XV	9·5	6·35	6·70	0·35			8·94	6·5
	XVI			6·70		9·26	5·5		
	XVII			6·68		8·86	6·0		
	XVIII	8·5	6·47	6·78	0·31	9·17	6·0		



III



IV

compound m.p. 81° to be the *syn* isomer existing in solution at room temperature predominantly in the *trans–syn–trans* conformation Ia.

The relative intensity of the Bohlmann bands in the isomer, m.p. 52° strongly suggests the *trans–anti–cis* (*cis–anti–trans*) stereochemistry (IIb = IIc). The *trans–anti–cis* conformation IIb on undergoing two nitrogen inversions and accompanying chair chair interconversions becomes the *cis–anti–trans* conformation IIc, identical with IIb. In this process the C6 axial proton in IIb becomes the C6 equatorial proton in IIc and the *trans* A:B–*cis* B:C junctions in IIb become *cis* A:B–*trans* B:C junctions in IIc. If, therefore, IIb (= IIc) is the predominant conformation for the *anti* isomer at room temperature then a singlet will be observed for the C6 methylene protons due to rapid interconversion between IIb and IIc. In fact (Table 3) the C6 methylene protons gave rise to a singlet at 6·65 τ and this observation coupled with the IR data confirms the *anti* stereochemistry of the low m.p. isomer and is evidence for the predominance of the *trans–anti–cis* (IIb = IIc) conformation at room temperature.

Methyl substituted perhydrodipyrido[1.2-c, 2′.1′-f]*pyrimidines.* In the case of the monomethyl derivatives of I and II there exists the additional stereochemical problem of determining the axial-equatorial nature of the Me substituent. Information regarding this may be obtained by observing the position of the centre of the Me doublet and the apparent J_{CH-Me} in the NMR spectrum since in the monomethylquinolizidines axial Me groups were found[17] to absorb at lower field and with a greater "J_{CH-Me}" than their equatorial counterparts. These correlations have also been found to exist in the perhydrodipyrido[1.2-*c*, 2′.1′-*e*]imidazole[10] and perhydropyrido[1.2-*c*]pyrrolo-[2′.1′-*e*]imidazole[7] series. In addition to the NMR data, evidence for the orientation of the Me group may be obtained from a study of the percentage of isomers obtained (Table 1) and assuming (with circumspection) the validity of Linstead's rule[18] of *cis*-addition of hydrogen to the Me substituted ring in the catalytic hydrogenation of the dipyridyl methane.

1-*Methyl perhydrodipyrido*[1.2-c, 2′.1′-f]*pyrimidines* (V, XII, *and* XIII). Three isomers of 1-methyl perhydrodipyrido[1.2-*c*, 2′.1′-*f*] pyrimidine were obtained in the ratio 55:30:15. The major isomer was assigned the *trans–syn–trans* stereochemistry on the basis of strong absorption in the 2800–2600 cm^{-1} region of the IR and the Δ of 0·98 ppm. The axial nature of the Me group was determined from the NMR parameters of the Me protons and from the expected *cis* relationship between the C1 and C12a hydrogens in the major isomer.

The remaining two isomers were readily assigned the *trans–anti–cis* stereochemistry from the IR evidence and from the singlet absorption for the C6 methylene protons in the one case and the small Δ of 0·46 ppm in the other. There are two possible diastereoisomers* of 1-methyl *anti* perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidine and

* All the perhydrodipyridopyrimidines exist either as racemates or in some cases optically inactive forms.

TABLE 4. 3000 cm^{-1}–2500 cm^{-1} REGION OF IR SPECTRA OF THE PERHYDRODIPYRIDO[1.2-*c*, 2′.1′-*f*]PYRIMIDINES

Compound no.	*Syn* isomers cm^{-1} (ε_a)	Compound no.	*Anti* isomers cm^{-1} (ε_a)
I	2822(99), 2783(186), 2745(91), 2732(120), 2672(91), 2638(56), 2591(41).	II	2820(91), 2786(96), 2767(101), 2750(69), 2737(61), 2718(54), 2690(69), 2660(49).
V	2822(82), 2792(153), 2741(96), 2680(61), 2660(58), 2640(46), 2600(43).	XII	2820(71), 2788(80), 2770(81), 2750(56), 2718(48), 2690(45), 2635(26).
VI	2825(91), 2790(174), 2738(105), 2677(82), 2640(55), 2600(34).	XIII	2820(70), 2790(81), 2772(80), 2695(49), 2660(38).
VII	2824(96), 2782(183), 2740(85), 2726(107), 2680(65), 2660(70), 2630(55), 2600(35).	XIV	2820(81), 2793(88), 2771(81), 2750(67), 2738(57), 2712(47), 2694(52), 2660(42).
VIII	2822(89), 2782(173), 2744(94), 2730(113), 2680(68), 2660(62), 2643(75), 2600(36).	XV	2820(69), 2780(83), 2761(69), 2720(51), 2680(44), 2650(34).
IX	2822(84), 2782(161), 2721(73), 2678(78), 2637(65), 2600(35).	XVI	2820(79), 2780(89), 2770(84), 2740(68), 2682(57), 2656(45).
X	2828(96), 2780(184), 2754(91), 2729(78), 2664(88), 2622(44), 2600(37).	XVII	2820(79), 2791(94), 2771(178), 2750(69), 2718(53), 2698(61), 2663(41).
XI	2828(94), 2781(181), 2729(78), 2668(83), 2624(42), 2600(36).	XVIII	2820(79), 2768(104), 2733(56), 2680(58), 2621(31).

the *trans–anti–cis* and *cis–anti–trans* conformations of these are shown in Fig. 5.

It can readily be seen that the two conformations (XIX and XX) of the *trans* 1H-12aH isomer suffer from the same number of non-bonded interactions and one would predict this compound to exist as a mixture of the two conformations in rapid equilibrium. Since the environment of the C6 methylene protons in both conformations is very similar a singlet absorption for these protons should be observed.

Conformation XXII of the *cis* 1H-12a*H* isomer is considerably destabilized by two severe interactions between the Me group and the C6 and C11a axial hydrogens whereas the alternative conformation XXI is free of any such interactions and the possible equilibrium must, therefore, be heavily weighted in favour of this conformation.

Thus the conformation XIX $\rightleftharpoons$ XX is assigned to the 1-Me isomer showing a singlet for the C6 methylene protons and XXI to that showing a quartet. This is supported by XXI possessing *cis* hydrogen atoms at C1 and C12a in accord with it being the

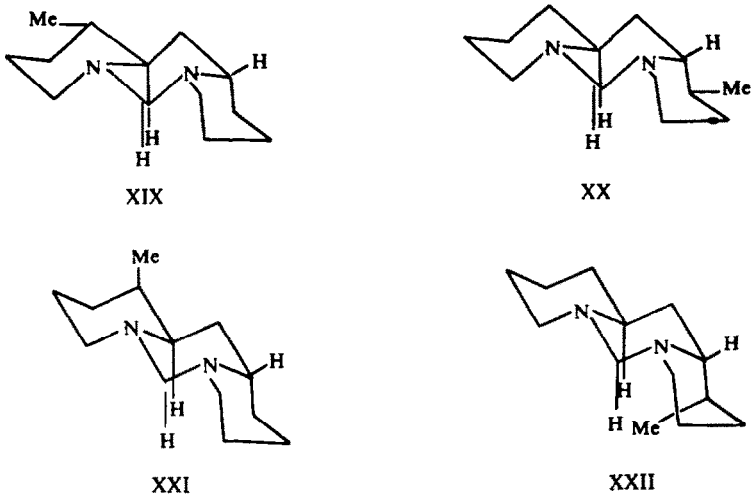
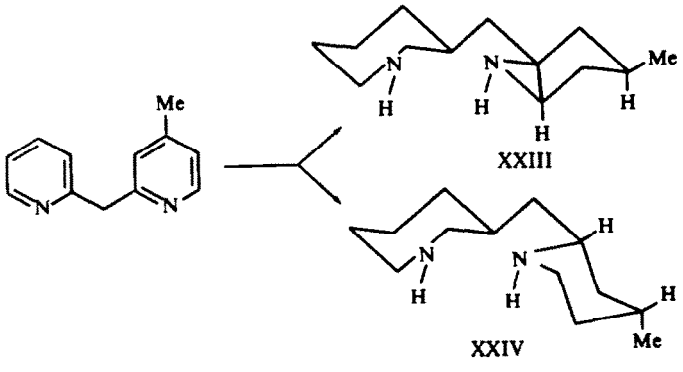


FIG 5. Conformations of 1-methyl-*cis*-1*H*, 12a*H* and of 1-methyl-*trans*-1*H*, 12a*H*, *anti* perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidine.

predominant *anti* isomer (Table 1). The NMR parameters of the Me protons (Table 2) are in agreement with these assignments.

2- *and* 4-*Methyl perhydrodipyrido*[1.2-c, 2′,1′-*f*]*pyrimidine* (VI, XIV, and IX, XVII). Only two isomers of the 2-Me compound were produced by the route shown in Fig. 3 and these were isolated in equal amounts. Catalytic hydrogenation of 2 pyridyl 2-(4 methylpyridyl) methane would be expected to yield the two diastereoisomeric



dipiperidyl methanes XXIII and XXIV as the major products corresponding both to *cis*-addition of hydrogen and the formation of the two thermodynamically most stable isomers. Thus on chemical grounds the two isomers of the tricyclic compounds obtained should be the *cis*-2*H*-12a*H*-2 methyl *syn* and *anti* perhydrodipyrido[1,2-*c*, 2′.1′-*f*]pyrimidines. In accord with these expectations the *syn* isomer (strong Bohlmann bands, $\Delta = 1{\cdot}04$ ppm) showed Me NMR parameters corresponding to an equatorial Me. The *anti* isomer gave a singlet for the C6 methylene protons resulting from the

rapid equilibrium between the *trans–anti–cis* and *cis–anti–trans* conformations, in which the environment of the C6 methylene protons is rather similar.

Similar arguments permitted the assignment of configuration and conformation to the two isomers of 4-methyl perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidine. In the case of the *cis*-4*H*-12a*H*-4-methyl *syn* isomer Δ was extremely large (1·60 ppm), a comparison with I showing that the Me group at C4 produces a shielding of H6ax by 0·19 ppm. and a deshielding of H6eq by 0·41 ppm. This confirms the stereochemistry XXV for the isomer since in an analogous pair of compounds the change from XXVI (X = O or NMe, R = H) to XXVI (X = O or NMe, R = Me) results in a deshielding of the C2 equatorial proton by ca 0·4 ppm and a shielding of the axial proton by ca 0·2 ppm.[7,8]

3-*Methyl perhydrodipyrido*[1.2-*c*, 2′.1′-*f*]*pyrimidine* (VII, VIII, XV, XVI). Two of the four isomers obtained were readily assigned the *trans–syn–trans* stereochemistry on the basis of intense Bohlmann bands in the IR and Δ values of 0·92 and 1·06 ppm. A decision regarding the orientation of the Me groups was made on the basis of the differences in the Me proton chemical shifts and apparent J_{CH-Me} values and confirmation of these assignments came from a knowledge of the relative proportions of the two isomers obtained by the synthetic route (Table 1). The two *anti* isomers were

TABLE 5. STERIC AND DIPOLAR INTERACTIONS IN SOME PERHYDRODIPYRIDO[1.2-*c*, 2′.1′-*f*]PYRIMIDINES

Compound	Conformation		Difference in interactions (*cis–syn–trans*)–(*trans–syn–trans*)
	trans–syn–trans	*cis–syn–trans*	
I, VI, VIII	d	2gb 1gp	2gb + 1gp − d
V	d 2gb 1gp	3gb 1gp	1gb − d
VII	d 1gb 1gp	2gb 1gp	1gb − d
IX	d 1gb	3gb 1gp	2gb + 1gp − d
X	d 2gb 2gp	1gb 2gp 2Me/Me	2Me/Me − (1gb + d)
XI	d 2gb	4gb 1gp	2gb + 1gp − d
	trans–anti–cis	*cis–anti–cis*	(*cis–anti–cis*)–(*trans–anti–cis*)
II	d 3gb	5gb 1gp	2gb + 1gp − d
XII	d 5gb 1gp	6gb 1gp	1gb − d
XV	d 4gb 1gp	5gb 1gp	1gb − d
XVIII (eq Me)	d 5gb	7gb 1gp	2gb − d
XVIII (ax Me)	d 4gb 2gp	3gb 2gp 2Me/Me	2Me/Me − (1gb + d)

obtained in equal amounts and stereochemical assignments were made using similar arguments to those employed in discussing the 1 and 2 Me *anti* compounds.

12-*Methyl perhydrodipyrido*[1.2-*c*, 2′.1′-*f*]*pyrimidine* (X, XI, XVIII). There are two possible *syn* isomers, but only one *anti* isomer of 12 methylperhydroidipyrido[1.2-*c*,

2′.1′-f]pyrimidine. The two *syn* isomers were recognised by their large *Δ* values and from the intensity of their IR absorption in the Bohlmann region. The *anti* isomer was assigned an equatorial Me from the values of "J_{CH-Me}" and the position of the centre of the Me doublet and the orientation of the Me groups in the *syn* isomers were assigned on the same basis.

(b) *Conformational equilibria in the perhydrodipyrido*[1.2-*c*, 2′.1′-*f*]*pyrimidines*

syn-*Perhydrodipyrido*[1.2-*c*, 2′.1′-*f*]*pyrimidine.* On the basis of very strong Bohlmann bands, large *Δ* values, and J_{gem} in the region of $-8{\cdot}5$ Hz all the *syn* isomers have been shown to exist predominantly in the *trans–syn–trans* conformation (Ia). However, an examination of the steric and dipolar interactions (Table 5) in these compounds suggest that two of the *syn* isomers should exist as equilibrium mixtures containing substantial amounts of the *cis–syn–trans* conformation in equilibrium with the *trans–syn–trans* conformation. In the construction of Table 5 only the most favourable *cis–syn–trans* and *cis–anti–cis* conformations (i.e. those in which the Me group is equatorial) were considered since, for example, the two possible *cis–syn–trans* conformations (Va and Vb) of the 1-methyl compound shown in fig. 6 differ in energy by 1 gauche butane +1 gauche propylamine interaction, and so the conformation with the axial Me-group (Va) may be neglected.

For the present purposes the major destabilising influences in a particular conformation are considered to be the dipolar interactions (d) arising when the two N lone pairs are *syn* axial, gauche butane (gb), and gauche propylamine (gp) interaction, and *syn* axial methyl–methylene interactions (Me/Me); no consideration is given to entropy changes.

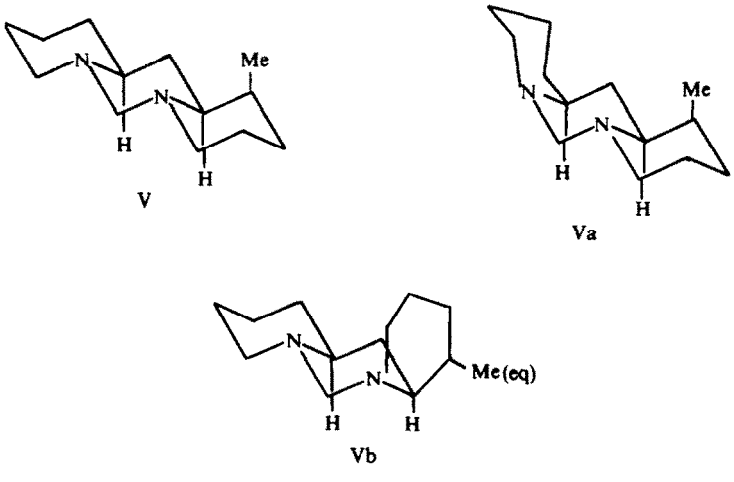
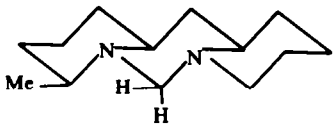
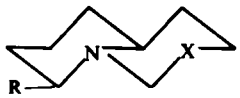


FIG 6. Conformations of 1 methyl *cis* 1*H*, 12a*H*-*syn* perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidine.

The discussion can only be qualitative since *inter alia*, the magnitudes of gp and d in these systems are not known and if there are significant deviations from chair geometry then the values of Me/Me and gb may be different from the analogous



XXV



XXVI

interactions in substituted cyclohexanes. It can be seen from Table 5 that the unsubstituted *syn* compound and those *syn* isomers in which the Me group is equatorial in the *trans–syn–trans* conformation are more stable in the *trans–syn–trans* than in the most favourable *trans–syn–cis* conformation by (2gb + gp − d). The 12-methyl *cis* 12*H*, 12a*H* compound (X) (axial Me in *trans–syn–trans*) is even more stable in the *trans–syn–trans* conformation by (2 Me/Me − [gb + d]). On the other hand, the remaining *syn* isomers in which the Me is axial when both ring fusions are *trans* are only more stable in the *trans–trans* than in the *cis–trans* conformation by (1gb − d). The expectation therefore is for the compounds I, VI, VIII–XI (Table 5) to exist as equilibrium mixtures containing at least 95% of the *trans–syn–trans* conformation and for the 1 methyl *cis* 1*H*, 12a*H*(V) and 3 methyl *cis* 3*H*, 12a*H* (VII) *syn* isomers to exist perhaps as equilibrium mixtures containing appreciable amounts of the *trans–syn–cis* in equilibrium with the *trans–syn–trans* conformation.

The general tenor of these expectations is supported by the values of J_{gem} for the C6 methylene protons. If values of J_{gem} of − 8·5 Hz and of − 11·5 Hz are taken as characteristic of 100% *trans–syn–trans* and of 100% *trans–syn–cis* respectively, then a J_{gem} of −9Hz would indicate an equilibrium mixture of 84% *trans–trans*:16% *cis–trans* conformations. It can be seen (Table 2) that in the particular pair of isomers (VII and VIII) the compound predicted to exist as a 95% *trans–syn–trans* equilibrium shows a J_{gem} of − 8·6 Hz, whereas the epimer, expected to contain much more *cis* conformation in the equilibrium mixture, shows a J_{gem} of −8·8 Hz.

Two of the *anti* compounds show a J_{gem} for the C6 methylene protons of −9·5 Hz and an examination of interactions in these (Table 5) leads to the expectation of substantial amounts of *cis–anti–cis* in equilibrium with the *trans–anti–cis* conformation. The J_{gem} of −9·5 Hz is in accord with this indicating a 70% *trans*:30% *cis* equilibrium. The position of equilibrium in the two *anti* perhydrodipyrido[1.2-*c*, 2′.1′-*f*]pyrimidines would therefore appear to be similar to that observed[8] for *trans*-10,6-*H*-3,10-dimethyl 1,3-diazabicyclo[4.4.0] decane (J = −9·9 Hz) and for the corresponding 3-t-butyl compound (J = −9·8 Hz) in which the difference in energy between the *cis* and *trans* fused ring conformations was also estimated to be (gp–d). Dipolar interactions in these tricyclic compounds would seem, therefore, to be an important factor in determining the position of conformational equilibria.

However, other factors[19] in addition to lone pair orientation can influence the value of J_{gem} and since the observed changes in J_{gem} in the syn series are small these could be a result of, for example, changes in bond angles caused by the axial/equatorial nature of the Me group in the *trans* conformations.

EXPERIMENTAL

Elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Micro-analytical Laboratory, Bonn, or the Organic Chemistry Dept., University of Reading. The NMR spectra were recorded as solutions in $CDCl_3$ on a Perkin–Elmer R.10 60 MHz spectrometer using TMS as internal reference. IR spectra were

measured as 0·1 M solutions in 0·5 mm cells in $CDCl_3$ on a Perkin–Elmer 457 Grating IR Spectrophotometer. Analytical GLC was performed on a Perkin–Elmer F.11 chromatograph, and preparative GLC on a Pye 105 Chromatograph.

Preparation of di(2-pyridyl) methanol and 2-pyridyl-2-(methylpyridyl) methanols

General procedure. A soln of n-BuBr (82·5 g, 0·6 mole) in ether (120 ml) was added with stirring to Li shavings (8·5 g, 1·2 mole) in ether (300 ml) at 0°, in an atmosphere of N_2. The mixture was then stirred for a further 1 hr when 2-bromopyridine (73·5 g, 0·4 mole) in ether (120 ml) was added over a period of 30 min to the butyl Li soln kept at −80°.

At the same temp pyridine-2-aldehyde or 6 methylpyridine-2-aldehyde (0·4 mole) in ether (120 ml) was added and the soln maintained at this temp for a further 2 hr. The temp of the soln was allowed to rise to room temp and then the soln was gently refluxed for 1 hr. The reaction mixture was decomposed by adding water (200 ml) and 35% HCl (200 ml), and the acidic layer separated and extracted twice with ether (2 × 300 ml). The acidic layer was neutralized with conc NaOH aq and extracted with ether (3 × 200 ml). The ether extract was dried, evaporated and the residue either recrystallized or distilled at reduced press.

Di(2-pyridyl) methanol (41 g) was obtained as a viscous yellow oil b.p. 115–117°/0·8 mm. (lit.[14] 143–144°/2 mm).

2-Pyridyl-2-(3-methylpyridyl) methanol (45 g) was obtained as colourless prisms m.p. 54–55° (from light petroleum (40–60°)). (Found: C, 71·78; H, 6·23; N, 14·30. $C_{12}H_9N_2O$ requires: C, 71·98; H, 6·04; N, 13·99%).

2-Pyridyl-2-(4-methylpyridyl) methanol (40 g) was obtained as a yellow oil b.p., 118–119°/1·0 mm n_D^{25}, 1·5764. (Found: C, 71·66; H, 6·08; N, 14·03. $C_{12}H_9N_2O$ requires: C, 71·98; H, 6·04; N, 13·99%).

2-Pyridyl-2-(5-methylpyridyl) methanol (45 g) was obtained as a viscous yellow oil b.p. 122–123°/1·5 mm n_D^{15}, 1·5639. (Found: C, 72·14; H, 6·23; N, 13·77. $C_{12}H_9N_2O$ requires: C, 71·98; H, 6·04; N, 13·99%).

2-Pyridyl-2-(6-methylpyridyl) methanol (40·4 g) was obtained as a pale yellow oil b.p. 103–106°/1·1 mm n_D^{15}, 1·5661. (Found: C, 71·78; H, 6·08; N, 14·24. $C_{12}H_9N_2O$ requires: C, 71·98; H, 6·04; N, 13·99%).

Di(2-pyridyl) chloro methane and the 2-pyridyl-2-(methylpyridyl) chloromethanes

General procedure. Thionyl chloride (28 g, 0·25 mole) in benzene (100 ml) was added to 2-pyridyl-2-(methylpyridyl) methanol (40 g) in benzene (500 ml) at 10° with vigorous stirring. No matter how vigorous the stirring the reaction mixture became a thick unstirrable syrup. The reaction mixture was heated gently for ½ hr. Water (200 ml) was added to the soln and the aqueous layer basified with conc NaOH aq. The alkaline soln was extracted with benzene (3 × 200 ml), and the extract dried and the benzene evaporated. Without exception the purple syrup-like crude products could not be distilled without decomposition, or induced to crystallize. The crude products were therefore used in the next stage.

Hydrogenolysis of the chloromethanes

General procedure. The crude 2-pyridyl-2(methylpyridyl) chloromethane (0·175 mole) was dissolved in glacial AcOH (250 ml) and powdered Zn (31 g) was added at room temp. The soln was heated on a water bath for 6 hr after which the inorganic residues were filtered off, and the filtrate reduced to 1/5th of its bulk by rotary evaporation. The soln was basified with conc NaOH aq, and extracted with ether (3 × 150 ml). The extracts were combined, dried, evaporated and the residue distilled under vacuum.

Di(2-pyridyl) methane (16 g) was obtained from di(2-pyridyl) chloromethane (40 g) as a colourless oil b.p. 104–106°/0·2 mm Lit.[14] b.p. 148–150°/3·5 mm).

2-Pyridyl-2-(3-methylpyridyl) methane (18·4 g) was obtained as a colourless oil b.p. 122–124°/0·9 mm n_D^{25}, 1·5764. (Found: C, 78·24; H, 6·37; N, 15·04. $C_{12}H_{12}N_2$ requires: C, 78·23; H, 6·57; N, 15·21%).

2-Pyridyl-2-(4-methylpyridyl) methane (17·6 g) was obtained as a colourless oil b.p. 110–113°/0·7 mm, n_D^{25}, 1·5812. (Found: C, 77·97; H, 6·40; N, 15·31. $C_{12}H_{12}N_2$ requires: C, 78·23; H, 6·57; N, 15·21%).

2-Pyridyl-2-(5-methylpyridyl) methane (20 g) was obtained as a colourless oil b.p. 120–122°/1·0 mm, n_D^{25} 1·5714. (Found: C, 78·22; H, 6·55; N, 15·15. $C_{12}H_{12}N_2$ requires: C, 78·23; H, 6·57; N, 15·21%).

2-Pyridyl-2-(6-methylpyridyl) methane (14 g) was obtained as a colourless oil b.p. 114–116°/0·5 mm, n_D^{25}, 1·5682. (Found: C, 78·14; H, 6·37; N, 15·44. $C_{12}H_{12}N_2$ requires: C, 78·23; H, 6·57; N, 15·21%).

Di(2-piperidyl) methane and the 2-piperidyl-2(methylpiperidyl) methanes

General procedure. A soln of the di(2-pyridyl) methane (16 g) in glacial AcOH (200 ml) was hydrogenated at 60 psi over PtO_2 catalyst (1 g). After the theoretical amount of H_2 had been taken up, the soln was

filtered and the filtrate evaporated to 50 ml. The soln was basified (NaOH aq) and extracted with ether (3 × 100 ml). The ether was evaporated and the residue distilled.

Di(2-piperidyl) methane (15g) was obtained as a colourless oil b.p. 90–91°/0·7 mm which solidified on cooling. Recrystallization from light petroleum (40–60°) gave colourless crystals m.p. 54–55°. (Found: C, 72·44; H, 11·94; N, 15·10. $C_{11}H_{22}N_2$ requires: C, 72·47; H, 12·16; N, 15·37%).

2-Piperidyl-2(3-methylpiperidyl) methane (13 g) was obtained as a colourless oil b.p. 88–90°/0·5 mm, n_D^{25}, 1·5089. (Found: C, 73·22; H, 12·37; N, 14·24. $C_{12}H_{24}N_2$ requires: C, 73·41; H, 12·32; N, 14·27%).

2-Piperidyl-2(4-methylpiperidyl) methane (15 g) was obtained from 2-pyridyl-2(4-methylpyridyl) methane (20 g) as colourless crystals m.p. 40–42° (from light petroleum). (Found: C, 73·38; H, 12·16; N, 14·31. $C_{12}H_{24}N_2$ requires: C, 73·41; H, 12·32; N, 14·27%).

2-Piperidyl-2(5-methylpiperidyl) methane (16 g) was obtained from 2-pyridyl-2(5-methylpyridyl) methane (20 g) as a colourless oil b.p. 96–98°/0·4 mm, n_D^{25}, 1·4977. (Found: C, 73·39; H, 12·21; N, 14·28. $C_{12}H_{24}N_2$ requires: C, 73·41; H, 12·32; N, 14·27%).

2-Piperidyl-2(6-methylpiperidyl) methane (14 g) was obtained from 2-pyridyl-2(6-methylpyridyl) methane (20 g) as a colourless oil b.p. 107–109°/0·8 mm, n_D^{25}, 1·4976. (Found: C, 73·33; H, 12·30; N, 14·37. $C_{12}H_{24}N_2$ requires: C, 73·41; H, 12·32; N, 14·27%).

Perhydrodipyrido[1.2-c, 2'.1'-f]*pyrimidines and the methylperhydrodipyrido*[1.2-c, 2'.1'-f]*pyrimidines*

General procedure. The di(2-piperidyl)methane (14 g) was shaken with 36% aqueous formaldehyde soln at room temp for 5 min. 30% NaOH aq was added, the mixture extracted with ether (3 × 200 ml) and the ether extracts were dried, evaporated and the residue distilled.

syn *and* anti- *Perhydrodipyrido*[1.2-c, 2'.1'-f]*pyrimidine* (I and II). A mixture of isomers (11 g) was obtained from di(2-piperidyl) methane (14 g), as a liquid b.p. 96–100°/0·6 mm which solidified. Details of the separation and the physical constants of the individual isomers of the tricyclic compounds are reported later in this experimental section.

1-*Methylperhydrodipyrido*[1.2-c, 2'.1'-f]*pyrimidine.* A mixture of isomers (8 g) was obtained from 2-piperidyl-2(3-methylpiperidyl) methane (11·5 g) as a colourless oil b.p. 104–106°/0·5 mm.

2-*Methylperhydrodipyrido*[1.2-c, 2'.1'-f]*pyrimidine.* A mixture of isomers (9 g) was obtained from 2-piperidyl-2(4-methylpiperidyl) methane (12·6 g) b.p. 85–87°/0·1 mm which solidified.

3-*Methylperhydrodipyrido*[1.2-c, 2'.1'-f]*pyrimidine.* A mixture of isomers (12 g) was obtained from 2-piperidyl-2(5-methylpiperidyl) methane (14·4 g) as a viscous oil b.p. 100–103°/0·4 mm.

4-*Methylperhydrodipyrido*[1.2-c, 2'.1'-f]*pyrimidines.* A mixture of isomers (9·5 g) was obtained from 2-piperidyl-2-(6-methylpiperidyl) methane (12·6 g) as a colourless oil b.p. 82–84°/0·4 mm.

Separation of the Isomeric Mixtures

syn *and* anti *Perhydrodipyrido*[1.2-c, 2'.1'-f]*pyrimidine*

Attempts to fractionally crystallize the mixture of isomers (10 g) from ether–light petroleum yielded one pure isomer, m.p. 81–82° (3 g) but the second isomer could not be obtained pure by crystallization. The mixture (6·5 g) was chromatographed over neutral alumina (Woelm activity I, 250 g) and the elution pattern is shown in Table 6. Separation was followed by analytical GLC.

The characteristics of the isomers are: t.s.t. m.p. 81–82°. (Found: C, 73·91; H, 11·33; N, 14·40%). t.a.c. m.p. 52–53°. (Found: C, 74·11; H, 11·38; N, 14·41: $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%).

1-*Methyl-perhydrodipyrido*[1.2-c, 2',1'-f]*pyrimidines*

The mixture shown to contain three isomers by analytical GLC was separated by preparative GLC using a 15ft × ⅜in. coiled glass column packed with Carbowax 20M (12½%) on 60–72 mesh chromosorb maintained at 180° and using N_2 as carrier gas at an inlet press of 70 psi, and a rate of 200 ml/min. The characteristics of the isomers are:

1-*Methyl*-cis-1H, 12aH t.s.t. b.p. 98–99°/0·50 mm, n_D^{25} 1·5127. (Found: C, 74·78; H, 11·70; N, 13·28. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

1-*Methyl*-cis-1H, 12aH t.a.c. b.p. 104°/0·5 mm, n_D^{25} 1·4914. (Found: C, 74·94; H, 11·61; N, 13·27. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

1-*Methyl*-trans-1H, 12aH t.a.c. b.p. 108–109°/0·50 mm, n_D^{25} 1·5064. (Found: C, 74·90; H, 11·92; N, 13·40. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

TABLE 6

Solvent	No. of fractions (100 ml)	Products	Wt (g)
Light petroleum (40–60°)	20	—	
Light petroleum + 1% ether	10	—	
Light petroleum + 2·5% ether	10	—	
Light petroleum + 5% ether	20	t.s.t.[a]	1·4 g
Light petroleum + 10% ether	10	t.s.t. + t.a.c.	1·2 g
Light petroleum + 25% ether	15	t.s.t. + t.a.c.	0·7 g
Ether	10	t.a.c.	0·5 g
Ether + 20% methanol	4	t.a.c.	2·2 g
			Recovery 6·0 g

[a] t.s.t. = *trans–syn–trans*, t.a.c. = *trans–anti–cis* perhydrodipyro[1.2-*c*, 2'.1'-*f*]pyrimidine.

2-Methyl-perhydrodipyrido[1.2-c, 2'.1'-f]*pyrimidines*

The isomeric mixture (5 g) shown to contain two isomers by analytical GLC was separated by column chromatography on neutral alumina (Woelm, act I, 200 g).

The 2-*methyl*-cis-2H, 12aH t.s.t. was obtained as a solid m.p. 75–76°. (Found: C, 74·80; H, 11·69; N, 13·06: $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

The 2-*methyl*-cis-2H, 12aH t.a.c. was obtained as a solid m.p. 46–47°. (Found: C, 75·00; H, 11·70; N, 13·15. $C_{13}H_{24}N_2$ requires: C, 74·94%; H, 11·61; N, 13·45%).

3-Methylperhydrodipyrido[1.2-c, 2'.1'-f]*pyrimidines*

The mixture was shown by analytical GLC to contain four isomers in approximately equal amounts. Preparative G.L.C. failed to separate the isomers because of the solid nature of the individual isomers and their very long retention times. The isomers were separated by column chromatography on neutral alumina (Woelm, activity I, 320 g). The mixture (8 g) was dissolved in light petroleum and added to the column, the separation was followed by analytical G.L.C.

The characteristics of the isomers are as follows:

3-*Methyl*-cis-3H, 12aH t.s.t. b.p. 94–95°/0·4 mm, n_D^{25} 1·5142. (Found: C, 74·88; H, 11·87; N, 13·27, $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

3-*Methyl*-trans-3H, 12aH t.s.t. m.p. 59–60°. (Found: C, 74·76; H, 11·81; N, 13·21. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

TABLE 7

Solvent	No. of fractions (100 ml)	Compound	Wt (g)
Light petroleum	20	—	—
Light petroleum + 1% ether	10	—	—
Light petroleum + 2·5% ether	10	—	—
Light petroleum + 5% ether	10	—	—
Light petroleum + 10% ether	10	—	—
Light petroleum + 20% ether	25	t.s.t.	2·1 g
Light petroleum + 50% ether	20	t.s.t. + t.a.c.	0·8 g
Ether	10	t.s.t. + t.a.c.	0·4 g
Ether + 10% methanol	5	t.a.c.	1·5 g
			Recovery 4·8 g

TABLE 8

Solvent	No. of fractions (100 ml)	3Me compound	Yield
Light petroleum	10	—	—
Light petroleum	30	*cis* 3H, 12aH t.s.t.	2·1 g
Light petroleum + 1% ether	10	*cis* 3H, 12aH t.s.t. + *trans* 3H, 12aH t.s.t.	0·3 g
Light petroleum + 2% ether	10	*cis* 3H, 12aH t.s.t. + *trans* 3H, 12aH t.s.t.	0·1 g
Light petroleum + 5% ether	15	*trans* 3H, 12aH t.s.t.	1·4 g
Light petroleum + 10% ether	10	—	—
Light petroleum + 20% ether	10	—	—
Light petroleum + 50% ether	10	—	—
Ether	12	*cis* 3H, 12aH t.a.c.	1·8 g
Ether + 1% methanol	10	*cis* 3H, 12aH t.a.c. + *trans* 3H, 12aH t.a.c.	0·7 g
Ether + 10% methanol	6	*trans* 3H, 12aH t.a.c.	1·2 g
		Recovery	7·6 g

3-*Methyl*-cis-3H, 12aH t.a.c. m.p. 57–58°. (Found: C, 74·84; H, 12·02; N, 13·49. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, N, 13·45%).

3-*Methyl*-trans-3H, 12aH t.a.c. m.p. 46–47°. (Found: C, 74·80; H, 11·90; N, 13·41. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

4-Methylperhydrodipyrido[1,2-c, 2'.1'-f]*pyrimidine*

The liquid mixture shown by analytical GLC to contain two isomers in equal amounts was separated by preparative GLC under the same conditions as those described for the separation of the 1-methylperhydrodipyrido[1.2-c, 2'.1'-*f*]pyrimidines. The isomers were characterized as follows:

4-*Methyl*-cis-4H, 12aH t.s.t. b.p. 76–77°/0·25 mm, n_D^{25} 1·5101. (Found: C, 74·70; H, 11·81; N, 13·27. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

4-*Methyl*-cis-4H, 12aH t.a.c. b.p. 84–85°/0·3 mm, n_D^{25} 1·4917. (Found: C, 74·83; H, 11·80; N, 13·32. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

Synthesis of the 12-*methylperhydrodipyrido*[1,2-c, 2'.1'-f]*pyrimidines*

1,1-*Di*(2-*pyridyl*) *ethan*-1-*ol.* A soln of n-BuBr (82·5 g) in ether (120 ml) was added with stirring to Li shavings (8·5 g) in ether (300 ml) at 0°, under an atmosphere of N_2. Stirring was continued for 1 hr, after which time 2-bromopyridine (73·5 g) in ether (120 ml) was added at a temp of − 80° over a period of 30 min. At the same temp 2-acetylpyridine (44 g) in ether (120 ml) was added and the temp maintained at − 80° for a further 2 hr. The soln temp was allowed to rise to room temp and the soln treated with water (200 ml) and 35% HCl (200 ml). The acidic layer was extracted with ether (2 × 300 ml), basified with conc NaOH aq, and the alkaline soln extracted with ether (3 × 150 ml). The ethereal extracts were combined, dried and the ether evaporated to leave a white solid (35 g) which on recrystallization from light petroleum 40–60° gave 1,1-di(2-pyridyl) ethan-1-ol as white plates m.p. 47–49°. (Found: C, 71·81; H, 5·93; N, 14·06; $C_{12}H_{12}N_2O$ requires: C, 71·98; H, 6·04; N, 13·99%).

1,1-*Di*(2-*pyridyl*) 1-chloroethane. 2,2-di(2-pyridyl) ethan-2-ol (32 g) was dissolved in benzene (500 ml) and the soln added with shaking to $SOCl_2$ (24 g) in benzene (150 ml), while the temp was kept constant at 10°. After allowing the mixture to stand at room temp for 2 hr water was added (150 ml) and the aqueous layer was neutralized with 30% NaOH aq, and extracted with benzene (3 × 200 ml). The extracts were

dried and the benzene evaporated to give 2,2-di(2-pyridyl) 2-chloroethane (25 g) as a thick syrup which was used without further purification.

1,2-Di(2-pyridyl) ethane. 1,1-di(2-pyridyl)1-chloroethane (25 g) was dissolved in glacial AcOH (200 ml) and powdered Zn (28 g) added gradually at room temp. The soln was heated on a water bath for 6 hr when the inorganic residues were filtered off and the glacial AcOH removed by rotary evaporation. The residual oil was treated with 30% NaOH aq and then extracted with ether (3 × 150 ml). The ether extracts were combined dried and evaporated, and the residue distilled to give 1,1-di(2-pyridyl)-ethane (21 g), b.p. 94–95°/0·25 mm, n_D^{25} 1·5794. (Found: C, 78·04; H, 6·55; N, 15·21; $C_{12}H_{12}N_2$ requires: C, 78·23; H, 6·57; N, 15·21%).

1,1-Di(2-piperidyl) ethane. 1,1-di(2-pyridyl) ethane (20 g) was hydrogenated (PtO_2 catalyst) in glacial AcOH (200 ml) under a pressure of 60 psi. After the calculated amount of H_2 had been taken up, the volume of the soln was reduced to 1/5th by rotary evaporation, the remaining soln made alkaline with 30% NaOH aq and extracted with ether (3 × 200 ml). The extracts were dried, the ether evaporated, and the residual oil distilled to give 1,1-di(2-piperidyl) ethane (15 g) b.p. 66–68°/0·07 mm, n_D^{25} 1·5051. (Found: C, 73·33; H, 12·19; N, 14·29. $C_{12}H_{24}N_2$ requires: C, 73·41; H, 12·32; N, 14·27%).

12-Methylperhydrodipyrido[1,2-c, 2',1'-f]pyrimidines

1,1-di(2-piperidyl) ethane (14 g) was shaken with 36% aqueous formaldehyde at room temp for 5 min, 30% NaOH aq was added to remove excess formaldehyde and the soln extracted with ether (3 × 150 ml). The ether extracts were combined, dried and the ether evaporated. The residual oil was distilled and the main fraction b.p. 100–102°/0·04 mm collected. This fraction shown to contain three isomers by analytical GLC (carbowax column), was separated on a 15 ft × ⅜ in glass column packed with chromosorb 60–80 mesh coated with 12½% Carbowax 20M. The characteristics of the three isomers are as follows:

12-Methyl cis 12H, 12aH t.s.t., white plates m.p. 54–55° (from 40–60° light petroleum). (Found: C, 74·54; H, 11·40; N, 13·38. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

12-Methyl-trans-12H, 12aH t.s.t., b.p. 84–85°/0·5 mm, n_D^{25} 1·5242. (Found: C, 74·68; H, 11·51; N, 13·44; $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

12-Methyl-t.a.c., b.p. 95–96°/0·5 mm, n_D^{25} 1·5171. (Found: C, 74·68; H, 11·54; N, 13·44. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

Acknowledgement—We thank the Science Research Council for a grant enabling us to purchase the Pye Chromatograph.

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