Studies of Chromenes. Part 4.[1] Oxidation of Hexahydro-5*H*-chromeno[3,4-*c*]-pyridazines and Conformational Isomerism in Tetra- and Hexa-hydro-*N*,*N*′-dialkoxycarbonyl-5*H*-chromeno[3,4-*c*]pyridazines

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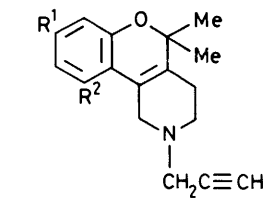
3,4-Bis(t-butoxycarbonyl)- and 3,4-bis(methoxycarbonyl)-8-methoxy-5,5-dimethyl-2,3,4,4a-tetrahydro-5*H*-chromeno[3,4-*c*]pyridazines and their 2,2-dimethyl analogues were hydrogenated to give hexahydrochromenopyridazines possessing only a *trans*-ring junction. Removal of the t-butoxycarbonyl groups from the *trans*-products afforded the corresponding 1,2,3,4,4a,10b-hexahydro-5*H*-chromeno[3,4-*c*]pyridazines which were oxidised first to 1,2,3,10b-tetrahydro- and then 1,2-dihydro-5*H*-chromenopyridazines. The last-named dihydro compounds possess an unusual [3,4]pyridazine hydrogenation pattern. The dialkoxycarbonyl derivatives of both the tetra- and hexahydrochromenopyridazines exist as pairs of conformational isomers whose interconversion is acid catalysed. The isomerism is considered to be due to restricted rotation about the less hindered N(3)–CO bond, the N(4)–CO bond being locked in one conformation by 1,3 interactions.

We have previously contrasted[1] the high stability of a chromenopyrazoline with simpler pyrazolines (dihydropyrazoles) which undergo elimination of nitrogen at or below room temperature.[2] We were interested to determine whether tetrahydro-5*H*-chromeno[3,4-*c*]pyridazines would show effects due to ring fusion since tetrahydropyridazines also generate alkenes[3] (and strained ring systems[4]) *via* nitrogen extrusion. Strained 3,4,5,6-tetrahydropyridazines, and those possessing a σ framework with a potentially high degree of π character, undergo nitrogen loss particularly easily;[5] an example related to the chromenopyridazines is 3,4,5,6-tetrahydro-3,6-diphenylpyridazine which gives styrene in competition with isomerisation to the hydrazone at 60 °C.[6] The biological activity of the cannabinols and of compound (**1**)[7] made chromenopyridazines of additional interest.

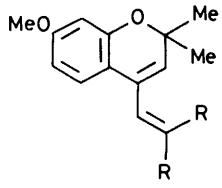
The vinylchromene (**2**; R=H) was obtained by dehydration of the alcohol resulting from the action of vinylmagnesium bromide on the chromanone. Cupric sulphate proved to be the best dehydrating agent, phosphoryl chloride giving only 16% of the required diene whilst the use of toluene-*p*-sulphonic acid or of iodine afforded only complex mixtures. The diene reacted readily with dimethyl azidocarboxylate to give the adduct (**3**) which was also obtained in almost theoretical yield when dehydration and addition were carried out simultaneously under catalysis by trifluoroacetic acid (TFA). Hydrogenation to give the hexahydrochromenopyridazine (**4**) was highly stereoselective, no diastereoisomers being detected by either t.l.c. or ^{1}H n.m.r. spectroscopy. The 4a-H n.m.r. signals,† identified by decoupling experiments, were split by only 8 Hz which is characteristic of coupling between *trans*-diaxial hydrogens. The hydrogen thus approaches from the side opposite the 4a-H_{ax} and models confirm that this hydrogen atom would be the controlling factor.

As has been found for a number of simpler 1,2-dialkoxycarbonylhydropyridazines,[8] hydrolysis of the dicarbamates (**3**) and (**4**) under relatively mild alkaline conditions removed only one methoxycarbonyl group from each compound. We took these to be the more accessible outer ones on N(3), the inner methoxycarbonyl groups on N(4) being severely hindered. Support for this assignment was available in the case of the tetrahydro derivative (**5**) which exhibited coupling between the NH moiety and the adjacent methylene group in its ^{1}H n.m.r. spectrum. The C(2) hydrogens appeared as an AB quartet split both by the olefinic 1-H and the amino hydrogens. On decoupling of the olefinic hydrogen, the lines of the C(2) methylene quartet appeared as doublets (*J* 3 and *J* 2.5 Hz) which collapsed to singlets on the addition of deuterium oxide. Removal of the remaining methoxycarbonyl group from the hexahydro derivative (**6**) occurred only under much more severe conditions than those previously reported (4M-potassium hydroxide in boiling ethanol; 2 h), *viz.* heating with 4M-potassium hydroxide in ethylene glycol at 150 °C for 4 h. Very little hydrolysis was observed with 0.8M-potassium hydroxide at 140 °C even after 10 h. The conditions required for complete hydrolysis are consistent with the reluctance of both N(4) and its associated carbonyl carbon to adopt sp^3 hybridisation (see later) and hydrolysis may proceed by alkyl–oxy fission.

The hexahydrochromenopyridazine (**7**), presumed to be the initial product of complete hydrolysis of compound (**4**), was



(**1**)



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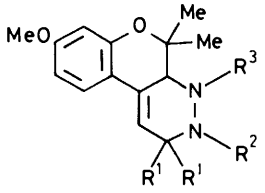
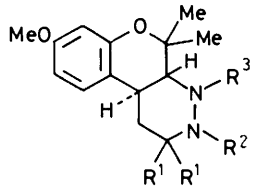
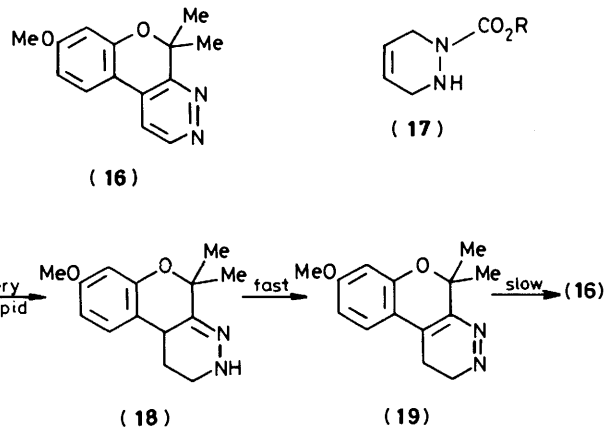




(**3**) R^1 = H, R^2 = R^3 = CO_2Me
(**4**) R^1 = H, R^2 = R^3 = CO_2Me
(**5**) R^1 = R^2 = H, R^3 = CO_2Me
(**6**) R^1 = R^2 = H, R^3 = CO_2Me
(**9**) R^1 = H, R^2 = R^3 = CO_2Bu^t
(**7**) R^1 = R^2 = R^3 = H
(**11**) R^1 = Me, R^2 = R^3 = CO_2Me
(**8**) R^1 = H, R^2 = R^3 = Me
(**13**) R^1 = Me, R^2 = R^3 = CO_2Bu^t
(**10**) R^1 = H, R^2 = R^3 = CO_2Bu^t
(**12**) R^1 = Me, R^2 = R^3 = CO_2Me
(**14**) R^1 = Me, R^2 = R^3 = CO_2Bu^t
(**15**) R^1 = Me, R^2 = R^3 = H

† The spectra were complicated by conformational isomerism, see later.



(16) (17) (18) (19) (20) (21) (22) (23) (24)

Scheme. Sequence of products from atmospheric oxidation of compound (7)

unstable under the conditions required and the only material isolated from the resultant mixture was the aromatised chromenopyridazine (**16**) which was obtained in 36% yield. There is evidence that under alkaline conditions 1,2-dialkoxycarbonylhexahydropyridazines undergo partial oxidation prior to hydrolysis;[9] however, this does not appear to occur to any appreciable extent in the present work since the monocarbamates were recovered largely unchanged after several hours under conditions just insufficient to effect hydrolysis.

In contrast to the hydrolysis of the dicarbamate (**4**), reduction of both methoxycarbonyl groups occurred readily with lithium aluminium hydride and afforded the *N,N'*-dimethyl derivative (**8**). We ascribe the facile reduction of the second methoxycarbonyl group, compared with its very slow hydrolysis, to intramolecular attack by an N(3)-complexed aluminium hydride derivative *via* a five-membered ring transition state.

In order to generate the hexahydropyridazine (**7**) under milder conditions the corresponding t-butoxycarbonyl derivatives (**9**) and (**10**) were prepared; hydrogenation was again so stereoselective that no diastereoisomers were detected. Removal of both the butoxycarbonyl groups from the hexahydro derivative (**10**) proceeded smoothly in TFA at room temperature.

The hexahydropyridazine (**7**) was stable under acidic conditions, but unstable as the free base, and ^{1}H n.m.r. spectroscopy showed that on standing in air at room temperature it rapidly lost one amino hydrogen and the C(4a) hydrogen. After 2 h the remaining amino hydrogen had also disappeared. Further change was much slower and even after 24 h no aromatisation had occurred (t.l.c. and the absence of a characteristic signal at δ 9.00). No olefinic signals were seen to develop during this time but we assigned a new multiplet at δ 3.2—3.4 to a C(2) methylene group and suggest the sequence shown in the Scheme, although no pure products could be isolated by chromatography. Mass spectrometry supported this sequence, the initial molecular ion of the hexahydro derivative (**7**) at *m/z* 248 being replaced first by ions at *m/z* 246 and 244 and then only at *m/z* 244. Only after the crude dihydro product (**19**) had been heated at 100 °C for 2 h did aromisation take place to an appreciable extent (t.l.c., n.m.r., and mass spectra).

Formation of the tetrahydro derivative (**18**) is unexceptional since 2,3,4,5-tetrahydropyridazines are the most stable of the three isomers usually found.[10] Thus, on removal of the alkoxycarbonyl group from compound (**17**), migration of the double bond gave 1,4,5,6-tetrahydropyridazine.[11] Similarly, oxidation of hexahydropyridazine with mercuric oxide initially gave 3,4,5,6-tetrahydropyridazine which then rearranged to 1,4,5,6-tetrahydropyridazine, the hydrazone form.[11-13] In the present work the preference for the hydrazone structure appears to be maintained even though conjugation with the aromatic ring is possible in two alternative structures. Although cyclic hydrazines are easily oxidised it is worth noting that the uncatalysed oxidation of hexahydropyridazine itself occurred only to the extent of 10% after 8 h at room temperature, compared with 100% after 20 min with platinum catalysis.[12]

The implied formation of the 3,4-dihydropyridazine (**19**) is unexpected, however, since this hydrogenation pattern is one of the three not normally found.[10] Only one case seems to be defined in the literature, namely compound (**20**), which is initially formed by dehydrohalogenation, but rearranges on heating to give the 2,3-dihydro isomer (**21**).[14] Isomerisation to a 1,2-, 1,4-, or 4,5-dihydro pattern, which would normally be more stable, in this instance is inhibited by the geminal alkyl substituents. In the absence of such inhibition 2,3-dihydropyridazines are isomerised by heat or alkali to the non-conjugated 1,4-form (**22**).[15] In the present work extended conjugation appears to control the positions of the double bonds in the dihydro derivative (**19**) in contrast to the tetrahydro case (**18**).

The relative difficulty in achieving the aromatisation of the dihydrochromenopyridazine (**19**) is also interesting since oxidation occurs readily with 1,4- and 1,2-dihydropyridazines.[14,16] The ease of oxidation of 4,5-dihydropyridazines is rather more dependent on the nature of any substituents.[10,17] Uncatalysed oxidation proceeds *via* abstraction of hydrogen from nitrogen (unlike the platinum-catalysed reaction which involves α-C–H abstraction)[12] and requires co-planarity of the lone-pair orbitals on the two nitrogen atoms for stabilisation of the resultant radical.[18] Conjugation in structure (**19**), which does not possess an amino hydrogen, may inhibit isomerisation to such an extent that aromatisation is slow.

In an attempt to support the sequence represented in the Scheme we also investigated the tetra- and hexa-hydrochromenopyridazines (**11**)—(**14**) which have the advantages of a limited number of isomers and simplified ^{1}H n.m.r. spectra and also possess increased steric compression (see later). Hydrogenation of the tetrahydrochromenopyridazines (**11**) and (**13**) was again virtually stereospecific. Removal of the butoxycarbonyl groups from the saturated product (**14**) afforded the hexahydrochromenopyridazine (**15**) which was more stable to atmospheric oxidation than the analogous compound (**7**), but could be readily oxidised with mercuric oxide. The major product, isolated in 80% yield, was not a tetrahydro- but a dihydro-chomenopyridazine (**23**). This structure was indicated by the absence of exchangeable protons and

Table 1. Isomer ratios and coalescence temperatures in various solvents

Compound	Isomer ratio and solvent					Coalescence temperature /°C
	CCl_4	$[^2H_8]PhMe$	$CDCl_3$	$PhNO_2$	$(CD_3)_2SO$	
(3)			1.6	1.3		100 ($PhNO_2$)
(11)	1.5	1.6	2.2		1.2	40 (Me_2SO)
						80 (PhMe)
(9)			6.0			
(13)	1.4	1.2	1.7		n/a*	20 (Me_2SO)
						80—100 (PhMe)
(4)			1.5		n/a*	20 (Me_2SO)
						90 ($CDCl_3$)
(12)		2.2	3.1		1.8	120 (PhMe)
(10)			6.5			
(14)		3.5	4.0		3.4	120 (PhMe)

* n/a indicates coalescence at room temperature.

of olefinic signals in the ^1H n.m.r. spectrum. A minor product (8%) was the 3,5-dihydro isomer (**24**), this structure being deduced from the absence of exchangeable protons but the presence of an olefinic signal (δ 5.9) and a signal (δ 4.18) assigned to 4a-H, each a narrow doublet. Both the dihydro derivatives (**23**) and (**24**) gave weak molecular ions at *m/z* 272 in the mass spectrometer, but the base peak ions appeared at *m/z* 257 indicating loss of a methyl group and consequent aromatisation. Rapid oxidation to a 3,4-dihydrochromenopyridazine is consistent with the sequence in the Scheme. No chromene was detected among the oxidation products of either of the hexahydrochromenopyridazines (**7**) and (**15**) although chromene formation was the major fragmentation in the mass spectrometer.

Apart from the unusual hydrogenation pattern found in the dihydrochromenopyridazines (**19**), (**23**), and (**24**) there is no indication that hydrochromeno[3,4-*c*]pyridazines are more stable than the hydropyridazines themselves. Oxidation of the tetrahydro derivatives appears to proceed to the exclusion of nitrogen elimination which suggests that the aromatic ring does not confer π stabilisation on the transition state for the reverse $[2_s + 2_a + 2_a]$ cycloaddition required by the *trans* ring junction. Such stabilisation is implied for 3,4,5,6-tetrahydro-3,6-diphenylpyridazine,[6] which does not, however, suffer the geometric constraints of the chromenopyridazine.

Conformational Isomerism.—All the dicarbamates described above occurred as isomeric mixtures undetected by t.l.c. but readily evident from their ^1H n.m.r. spectra. Two distinct m.p. ranges were also observed. Neither the *N,N'*-dimethyl derivative (**8**) nor the monocarbamates (**5**) and (**6**) exhibited isomerism. These isomers were regarded as conformational since, when heated to *ca.* 100 °C, pairs of signals in the ^1H n.m.r. spectra coalesced, the original pairs being re-formed on cooling (Figure 1). Coalescence temperatures are recorded in Table 1. The observed isomer ratios varied slightly from solvent to solvent (Table 1), the most extreme case being the tetrahydrotetramethyl derivative (**11**) which gave only one set of ^1H n.m.r. signals in $(CD_3)_2SO$, although indications of isomerism were still evident from the rather broad lines (Figure 2). In this solvent the spectrum at 20 °C closely resembled that of the same compound in $[^2H_8]$toluene at 80 °C. The intermediate nature of the spectrum in Me_2SO shows that the conformational barrier has been lowered and that one isomer has not been preferentially stabilised to the exclusion of the other isomer. Interestingly, the bis(butoxycarbonyl)hexahydro analogue (**14**) did not show this effect, indicating a significantly higher energy barrier (also evident from the higher coalescence temperature) for this sterically congested molecule.

Conformational isomerism in hydrochromenopyridazines may involve ring inversion, inversion at nitrogen, or restricted rotation about the N–CO bonds. Despite much study early uncertainty concerning the assignment of specific processes to particular energy barriers continues.[19,20] It does not seem to have been stressed that in dialkoxycarbonylhydropyridazines in particular there is 'inverse co-operation' both between the two carbamate groups and between the inversion and rotation of one carbamate group. That is, if steric or electronic effects cause one nitrogen atom to become more highly sp^2 hybridised, say, then the positive charge on that nitrogen increases the tendency for the adjacent nitrogen atom to adopt sp^3 hybridisation. Within one carbamate group the introduction of large 1,2- or 1,3-steric interactions, for example, would disfavour a tetrahedral nitrogen relative to its transition state for inversion whilst at the same time favouring the rotamers with respect to the rotational transition state. The inversion barrier would thus be reduced whilst the rotational barrier would be increased. Steric interactions in hydropyridazines are particularly large because of the shorter bonds involving nitrogen;[21] thus, whether inversion or rotation has the higher barrier is sensitive to the particular situation and makes assignments based on a numerical comparison of published data suspect.

The compounds under discussion can only undergo a half-ring inversion leading to a boat form. Whilst boat forms can be conformationally preferred in fused systems under certain circumstances (*e.g.* the decalones), models of the chromenopyridazines described here suggest that strong 1,2-, 1,3-, or 1,4-interactions (depending on the hybridisations assigned to the two nitrogen atoms) would result. Even in the less hindered perhydroquinolines, the *trans*-forms showed no conformational changes whilst the *cis*-forms did[22] so that ring inversion in the present case is strongly discounted.

The absence of isomerism in the *N,N'*-dimethyl compound (**8**) suggests that inversion at nitrogen is not responsible for the isomerism since the barriers for these modes have been found to be similar within a given system for both methyl and methoxycarbonyl substituents.[23] It also implies that the isomerisation depends on the nitrogen atoms possessing appreciable sp^2 character, which is also required for restricted rotation. In order to gain evidence for this conclusion we examined the changes induced by the addition of TFA in the ^1H n.m.r. spectra of several of the compounds.

Protonation was found to remove isomerism in most cases, as has been found for rotational isomerism in many amides and

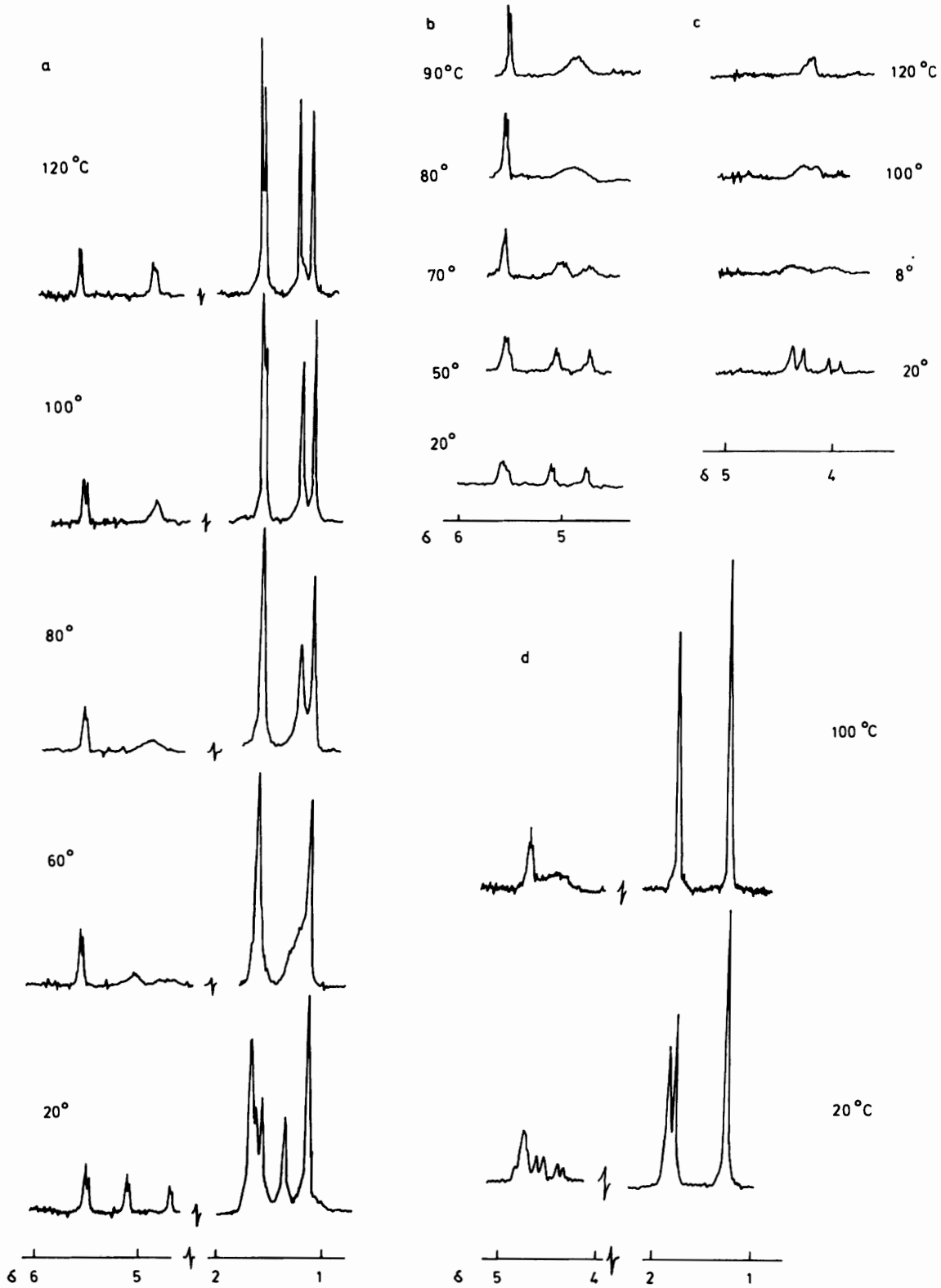


Figure 1. Temperature dependence of ^{1}H n.m.r. spectra. (a) (**11**), toluene, 90 MHz; (b) (**13**), toluene, 90 MHz; (c) (**12**), toluene, 90 MHz; (d) (**3**), nitrobenzene, 60 MHz

carbamates.[24] Jackman *et al.*[25] have shown that although *O*-protonation of amides is energetically favoured,[26] catalysis of rotation arises from *N*-protonation; moreover, *N*-protonation is more likely in carbamates.[27] Ring inversion, if anything, should be hindered by *N*-protonation whilst inversion at nitrogen should be completely frozen, the opposite of the observed effect. *O*-Protonation is not expected to alter any of the modes significantly, but should increase the rotational barrier somewhat because of the greater resonance energy.

The effects of TFA on the ^{1}H n.m.r. spectra of compounds

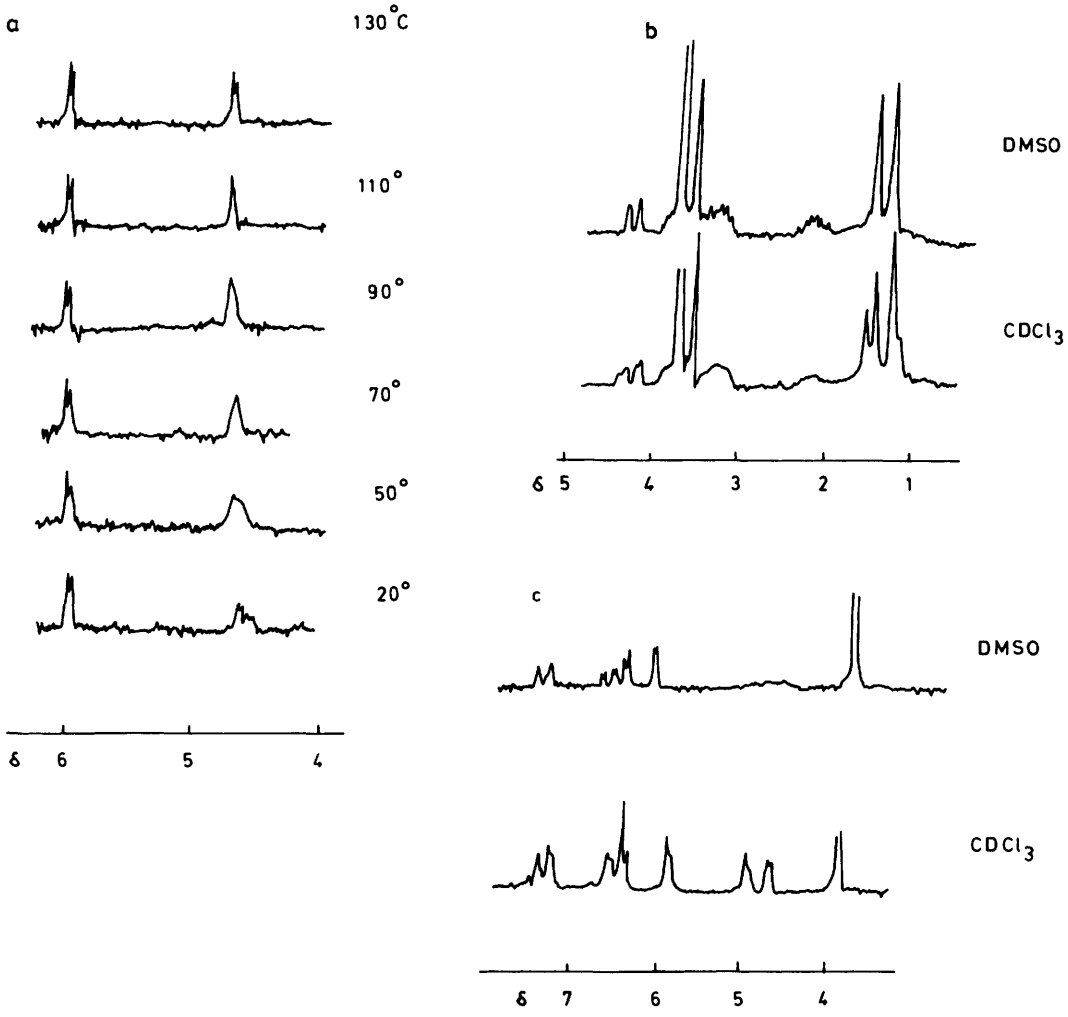


Figure 2. ^{1}H N.m.r. spectra in $(CD_3)_2SO$. (a) (**11**), 90 MHz, with temperature variation; (b) (**4**), 60 MHz, compared with spectrum in $CDCl_3$; (c) (**13**), 60 MHz, compared with spectrum in $CDCl_3$

(**3**), (**4**), (**11**), and (**12**) are reproduced in Figure 3 (it was not possible to investigate the butyl derivatives). Isomerism was monitored by the 4a-H or the methyl signals, though the latter were often coincident. In the spectrum of the tetrahydrotetramethyl derivative (**11**) the only sign of isomerism was a shoulder on one of the methyl signals. The gradual addition of TFA first gave a more complex pattern before finally simplifying the signals. This simplification of the spectrum was not due to an extreme isomer ratio[28] as the single signals, apart from being broad, appeared between the individual isomer signals. It is apparent that, in this more hindered molecule, rotation is slower (or at least protonation is less probable), intermediate levels of TFA giving rise to spectra similar to those of the same compound at 80—90 °C in [$^2H_8$]toluene. An even higher rotational barrier is evident in the most hindered of the compounds studied in this way, the hexahydrochromenopyridazine (**12**); the beginning of coalescence of the 4a-H signals required 30% TFA in this compound, compared with just 3% for the less hindered molecules (**3**) and (**4**). The coalesced lines showed no sign of sharpening even in 66% TFA. On removal of the acid (by washing with aqueous sodium hydroxide or passing through alumina) the original spectra were obtained in all cases. Acidic catalysis thus seems to be very sensitive to steric hindrance and differentiates electronic and steric contributions to rotational barriers.

Acidic catalysis implies that rotation is indeed the conformational mode responsible for isomerisation in these hydrochromenopyridazines. The presence of two carbamate groups should therefore lead to the existence of four rotamers, but only two were observed for each of the compounds, though it is possible that other conformers were present in undetectable proportions. This implies either that one carbamate group in each example has a much lower energy barrier or that there are structural features which thermodynamically strongly favour just one conformer for one of the groups.

Our preferred explanation for the limited conformational isomerism found is that there is restricted rotation about only the outer of the N–CO bonds and that the inner carbamates are locked into one conformation. Models clearly show that the inner N(4) atoms would indeed be very reluctant to adopt sp^3 hybridisation because of severe 1,3 interactions with one or other of the two 5-methyl groups [and with a 2-methyl group in compounds (**11**) and (**14**)] whereas sp^2 hybridisation at N(4) relieves these interactions (see Figure 4). We therefore believe that the N(4) carbamate groups are locked in the conformation shown, with the carbonyl oxygen, rather than the alkoxy group, being directed between the two 5-methyl groups. This explanation accounts for the particular reluctance of the monocarbamates (**5**) and (**6**) to undergo hydrolysis since this would require both N(4) and the associated carbonyl carbon to become tetrahedral.

In general the magnitude of solvent effects on rotational

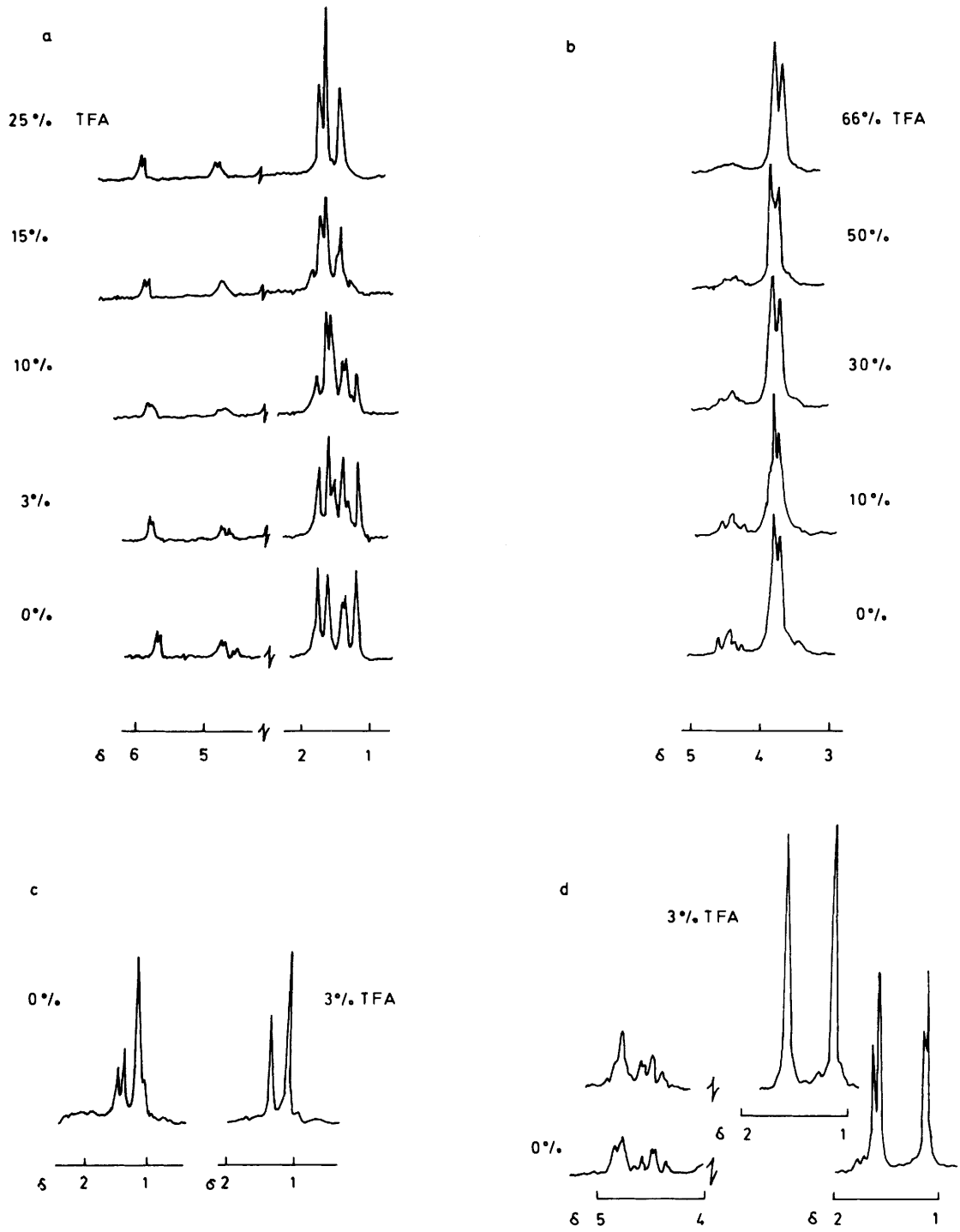


Figure 3. Effect of TFA on the ^{1}H n.m.r. spectra. (a) (**11**); (b) (**12**); (c) (**4**); (d) (**3**); all in $CDCl_3$ at 60 MHz

barriers is small[29] though polar solvents tend to increase the barriers[25,30] so that the behaviour of the compounds in Me_2SO is surprising. Nevertheless it is consistent with our interpretation since we have observed the removal of rotational isomerism in several formanilides, where only rotation is relevant, in this solvent.

The highest isomer ratios observed (*ca.* 6:1) are those of the dibutylcarbamates (**9**) and (**10**). If the inner, N(4), carbamate groups of these two compounds are indeed locked with their butoxy groups directed towards the N(3) carbamate groups then it is not surprising that the favoured rotamers are those in which the N(3) carbamate butoxy groups avoid those of the inner group. Moreover, as steric compression is increased on the other side of N(3) by the C(2) *gem*-dimethyl groups, then this tendency becomes less advantageous and the isomer ratio falls to 4.0:1 in the case of (**14**) and even to *ca.* 1.5:1 in the case of the less flexible tetrahydro derivative (**13**).

The above interpretation implies that the outer N–CO bonds should have a smaller degree of π character than the inner and that these differences might be reflected in the i.r. absorption

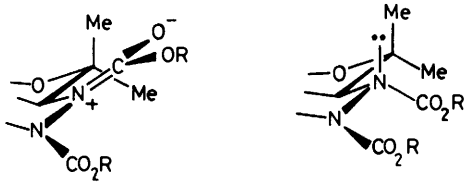
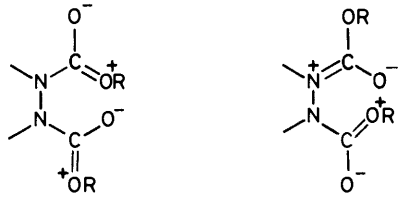


Figure 4. Conformations of the $N(4)CO_2R$ group with respect to the 5-methyl groups with sp^2 and sp^3 hybridisation at N(4)



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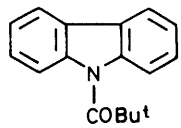
frequences of the carbonyl groups. Unfortunately the situation is not that clear since two carbonyl frequencies have been observed for both cyclic (solid and solution) and linear (solid) symmetrical dialkoxycarbonylhydrazides and even for a monoalkoxycarbonyl-1,2,3,6-tetrahydropyridazine.[20,31] This doubling has been attributed both to Fermi resonance and to field effects and used as evidence for ester resonance, as in structure (**25**).[31] Evidence for this detailed structure is sparse however and indeed structure (**26**) seems more likely and avoids the juxtaposition of two positively charged nitrogen atoms as effectively. It may be that the lowering of the barrier in Me_2SO is related to the stabilisation of such an ester resonance form and the aprotic nature of the solvent.

In most cases the compound under discussion exhibited two carbonyl bands both in chloroform and potassium bromide. Differences were more pronounced in the solid state (Table 2) but, because of the difficulties referred to earlier, interest centred on the relative positions of the bands from one compound to another. For all the compounds one band appeared within the range 1 685—1 710 cm^{-1} and we assign this band to the inner carbamate group. The second band occurred over a wider range (1 692—1 745 cm^{-1}) in the solid state than in chloroform (1 702—1 723 cm^{-1}) and assignment of this band to the outer carbamate would be consistent with the greater freedom of this group to react to its steric environment. The data for compound (**14**) were among the more extreme *cf.* Me_2SO, again reflecting the severe hindrance in this molecule which leads to a greater degree of π character in the outer N–CO bond.

The systems described here appear to us to be interesting examples of conformational locking comparable to that found in *ortho* disubstituted benzamides and anilides where rotational barriers as high as 125—135 kJ/mol have been estimated.[32] In most examples of this type steric hindrance reduces resonance by preventing co-planarity and thereby reduces the rotational barrier. In extreme cases, for example the *N*-acylcarbazole (**27**),[33] no rotation is observed, the butylcarbonyl group being held perpendicular to the aromatic plane, and in these systems amide rotation is much slower than ring inversion or inversion at nitrogen.[34] If correct, our interpretation of the conformational isomerism observed in the present work provides an example in the opposite sense, that of steric hindrance locking the amide resonance form. We have not carried out more detailed analyses of these chromenopyridazines (line shape analysis, ^{13}C, ^{14}N, and ^{17}O n.m.r.,

Table 2. I.r. carbonyl frequencies

Compound	ν_{CO}/cm^{-1} KBr	5% $CHCl_3$
(**3**)	1 710—1 730	
(**11**)	1 705—1 735	1 708
		1 720
(**9**)	1 685—1 710	1 699
(**13**)	1 708	1 720
	1 728	1 708
(**4**)	1 695	1 723
	1 735	1 705
(**12**)	1 700	
	1 725	1 706
(**10**)	1 695	1 721
		1 695
(**14**)	1 692	1 712sh
	1 720	1 691
		1 702



(27)

photoelectron spectroscopy) as we would require substrates without the 8-methoxy group, and with incorporated deuterium in order to reduce overlap of important minor signals.

Experimental

M.p.s are uncorrected. I.r. spectra were recorded on a Hilger and Watts Infrascan. U.v. spectra were determined with a Perkin-Elmer model 137 spectrometer. Routine (60 MHz) n.m.r. spectra were obtained on a Varian EM 360 or Perkin-Elmer R24 machine with tetramethylsilane as internal standard. 90 MHz Spectra were recorded on a Bruker HXE 90 instrument and 300 MHz spectra on a Bruker WM 300/WB spectrometer. Higher field spectra were used to assign signals as this was difficult at 60 MHz because of the existence of isomers, even with decoupling. Mass spectra were obtained on a MS9 instrument. The homogeneity of compounds was established by t.l.c. in at least three solvent systems of differing polarities. Ether refers to diethyl ether.

7-Methoxy-2,2-dimethyl-4-vinyl-2H-chromene (**2**; R = H).—(*a*) A solution of 7-methoxy-2,2-dimethyl-4-vinylchroman-4-ol[34] (3.0 g, 12.8 mmol) in dry benzene (100 ml) was boiled under reflux in the presence of anhydrous cupric sulphate (2.0 g) with azeotropic removal of water for 30 min. The benzene solution was filtered, washed with sodium hydrogen carbonate solution and then water, and dried ($MgSO_4$). Removal of the solvent left a dark oil which was purified by silica-gel chromatography (benzene–light petroleum as eluant) to give the title compound (2.1 g, 76%) as a chromatographically homogeneous (t.l.c.) *oil*; $\nu_{max.}$ (film) 1 630sh, 1 615, 1 570, and 1 507 cm^{-1}; $\lambda_{max.}$(EtOH) 212 (ε 16 000 dm^3 mol^{-1} cm^{-1}), 228sh (1 100), 270 (5 000), and 310 nm (3 700); δ ($CDCl_3$) 1.38 (6 H, s), 3.70 (3 H, s), 5.17 (1 H, dd, *J* 2 and 10 Hz), 5.47 (1 H, dd, *J* 2 and 17 Hz), 5.52 (1 H, s), 6.25—6.80 (3 H, m, 2 × ArH + C*H*=CH_2), and 7.10 (1 H, d, *J* 8 Hz) (Found: M^+, 216.1133. $C_{14}H_{16}O_2$ requires *M*, 216.1150).

(*b*) To a solution of the chromanol (0.20 g, 0.85 mmol) in anhydrous pyridine (5 ml) was added phosphoryl chloride (1.5 ml) dropwise with stirring at 0 °C. The mixture was stirred at room temperature for 48 h, poured into ice–water, and extracted with ether. The ethereal solution was washed successively with 1M-hydrochloric acid and water. Evaporation of the dried ($MgSO_4$) extract and silica-gel chromatography afforded the diene (**2**; R = H) (0.03 g, 16%) (t.l.c. and n.m.r.).

(*c*) The chromanol (0.20 g, 0.85 mmol) in dry benzene (20 ml) was boiled with a catalytic amount of toluene-*p*-sulphonic acid under azeotropic conditions. Work-up after 1 min afforded an oil (0.16 g) which consisted of a complex mixture of products (t.l.c. and n.m.r.).

(*d*) The chromanol (0.20 g) in dry benzene (20 ml) was boiled under reflux in the presence of a catalytic amount of iodine for 30 min. Work-up afforded a dark oil which contained a complex mixture of products (t.l.c. and n.m.r.).

8-*Methoxy*-3,4-*bis*(*methoxycarbonyl*)-5,5-*dimethyl*-2,3,4,4a-*tetrahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**3**).—(*a*) A solution of the diene (**2**; R = H) (0.500 g, 2.3 mmol) in dichloromethane (10 ml) was added to a solution of dimethyl azodicarboxylate (0.336 g, 2.3 mmol) in dichloromethane (10 ml). After 1 h the solvent was removed to leave a gum which solidified on storage at 0 °C. Recrystallisation from chloroform–light petroleum afforded a mixture of two components (*ca.* 2:1, by n.m.r. spectroscopy) but fractionation by chromatography was unsuccessful and the product was characterised as a homogeneous mixture of isomers of the title tetrahydropyridazine (**3**) (0.783 g, 94%) as colourless *needles*, m.p. 132—138 °C (some melts at 132 °C but most at 136 °C); $\nu_{max.}$(KBr) 1 705—1 745, 1 615, 1 575, and 1 505 cm^{-1}; $\lambda_{max.}$(EtOH) 219 (ε 23 000 dm^3 mol^{-1} cm^{-1}), 262 (14 800), 265sh (14 600), 303 (6 800), and 309sh nm (6 500); δ ($CDCl_3$) 1.12 and 1.59 (major) and 1.15 and 1.63 (minor) (total 6 H, 4 × s, *gem*-Me_2), 3.75—3.77 (10 H, 3 × 2 + 1 m, 3 × OMe + one 2-H), 4.2—4.6 (1 H, dd, *J* 8 and 6 Hz, other 2-H, major and minor), 4.75 (major) and 4.82 (minor) (total 1 H, 2 × d, *J* 2 Hz, 4a-H), 6.07—6.30 (1 H, ddd, *J* 6, 2, and 2 Hz, 1-H, major and minor), 6.30—6.60 (2 H, m), and 7.30 (1 H, d, *J* 8 Hz) (irradiation at δ 6.17 caused the signal δ 4.2—4.6 to collapse to a doublet, *J* 8 Hz and that at 4.75—4.82 to sharpen and irradiation at δ 4.4 caused the signal at δ 6.07—6.30 to simplify to a dd) (Found: C, 59.3; H, 6.5; N, 7.45%; M^+, 362.1511. $C_{18}H_{22}N_2O_6$ requires C, 59.65; H, 6.12; N, 7.73%; *M*, 362.1478).

(*b*) A solution of the vinylchromanol (0.200 g, 0.85 mmol) and dimethyl azodicarboxylate (0.125 g, 0.85 mmol) in dry benzene (30 ml) was boiled under azeotropic conditions with anhydrous cupric sulphate (0.300 g). Work-up after 1 h afforded a dark gum which gave the tetrahydropyridazine (**3**) (0.206 g, 67%) after purification by chromatography.

(*c*) To a solution of the vinyl chromanol (0.200 g, 0.85 mmol) in dichloromethane (15 ml) containing dimethyl azodicarboxylate (0.125 g, 0.85 mmol) was added trifluoroacetic acid (1 drop). After 1 h the solvent was evaporated to leave the tetrahydropyridazine (**3**) (0.305 g, 99%) as the only product (t.l.c. and n.m.r.).

8-*Methoxy*-3,4-*bis*(*methoxycarbonyl*)-5,5-*dimethyl*-trans-1,2,3,4,4a,10a-*hexahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**4**).—The tetrahydropyridazine (**3**) (0.800 g, 2.21 mmol) in ethanol (30 ml) was hydrogenated in the presence of palladium on charcoal (0.08 g). After 1 h the solution was filtered through Hi-flow and the solvent evaporated to afford an isomeric mixture of the title hexahydropyridazine (**4**) as a homegeneous (t.l.c.) *gum* (0.772 g, 96%); $\nu_{max.}$(film) 1 695—1 735, 1 620, 1 585, and 1 505 cm^{-1}; $\lambda_{max.}$(EtOH) 211 (ε 15 000 dm^3 mol^{-1} cm^{-1}), 225sh (5 000), 284 (2 200), and 290 nm (2 000); δ ($CDCl_3$) 1.28 and 1.48 (major) and 1.28 and 1.58 (minor) (total 6 H, 3 × s, *gem*-Me_2), 1.63—2.55 (2 H, m, 2-H_2), 3.10—3.50 (3 H, m, C*H*CH_2CH_2N), 3.50—3.9 (9 H, 3 × OMe, major 3.67, s, minor 3.55, s), 4.31 (major) and 4.35 (minor) (total 1 H, both d, *J* 8 Hz, 4a-H), 6.23—6.58 (2 H, m), and 7.0 (1 H, d, *J* 8 Hz) (Found: M^+, 364.1624. $C_{18}H_{24}N_2O_6$ requires *M*, 364.1634).

Alkaline Hydrolysis of the Tetrahydrochromenopyridazine (**3**).—(*a*) The tetrahydrochromenopyridazine (**3**) (0.200 g, 0.55 mmol) in 50% aqueous ethanol (5 ml) was boiled under reflux with 30% potassium hydroxide solution (5 ml). After 20 min the cooled mixture was diluted with ethyl acetate (40 ml) and washed with water (3 × 20 ml). Evaporation of the dried ($MgSO_4$) solvent afforded 8-*methoxy*-4-*methoxycarbonyl*-5,5-*dimethyl*-2,3,4,4a-*tetrahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**5**) (0.124 g, 74%) as a homogeneous (t.l.c.) foam; $\nu_{max.}$(film) 3 440, 3 300, 1 700, 1 620, 1 580, and 1 505 cm^{-1}; $\lambda_{max.}$(EtOH) 220 (ε 18 000 dm^3 mol^{-1} cm^{-1}), 229sh (13 000), 235sh (10 000), 262 (14 000), 267sh (13 000), 306 (6 500), and 311sh nm (6 000); δ ($CDCl_3$) 1.17 and 1.53 (each 3 H, s), 3.75 (6 H, s), 3.83 (1 H, s, 4a-H), 4.05—4.38 (2 H, m, 2-H_2), 4.57 [1 H, br, N(3)H], 6.02 (1 H, br m, 1-H), 6.33 (1 H, d, *J* 2 Hz), 6.38 (1 H, dd, *J* 2 and 8 Hz), and 7.27 (1 H, d, *J* Hz) (addition of deuterium oxide caused the signal at δ 4.57 to disappear and that at 4.05—4.38 to sharpen. Irradiation at 6.02 caused the signals at 4.05—4.38 to collapse to two pairs of doublets, one *J* 3 Hz the other *J* 2½ Hz, which in turn collapsed to an ABq, *J* 12 Hz, on the addition of deuterium oxide) (Found; M^+, 304.1401. $C_{16}H_{20}N_2O_4$ requires *M*, 304.1423).

(*b*) The above experiment was repeated but the mixture boiled for 4 h. Work-up afforded the above monocarbamate (**5**) as the only product (t.l.c. and n.m.r.).

Alkaline Hydrolysis of the Hexahydrochromenopyridazine (**4**).—(*a*) The hexahydrochromenopyridazine (**4**) (0.200 g, 0.55 mmol) in 30% ethanolic potassium hydroxide solution (8 ml) was boiled under reflux for 2 h under nitrogen. Work-up as above afforded 8-*methoxy*-4-*methoxycarbonyl*-5,5-*dimethyl*-trans-1,2,3,4,4a,10b-*hexahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**6**) (0.138 g, 82%) as a homogeneous (t.l.c.) foam; $\nu_{max.}$(film) 3 380, 1 700, 1 611, 1 592, and 1 502 cm^{-1}; $\lambda_{max.}$(EtOH) 210 (ε 22 000 dm^3 mol^{-1} cm^{-1}), 224sh (7 000), 283 (2 000), and 289nm (1 900); δ ($CDCl_3$) 1.22 and 1.55 (each 3 H, s, *gem*-Me_2), 1.93—4.37 (7 H, m, saturated CH + NH), 3.70 and 3.73 (each 3 H, s, 2 × OMe), 6.32—6.63 (2 H, m), and 7.12 (1 H, d, *J* 9 Hz) (addition of deuterium oxide caused simplification of the signals at δ 2.9—4.30) (Found: M^+, 306.1598. $C_{16}H_{22}N_2O_4$ requires *M*, 306.1579).

(*b*) The hexahydro derivative (**4**) (0.200 g, 0.55 mmol) in ethylene glycol (5 ml) was heated to 100 °C whilst a slow stream of nitrogen was passed through the solution. Potassium hydroxide pellets (4.00 mmol) were added and the mixture heated at 140 °C. After 10 h ether (20 ml) was added to the cooled mixture and the organic layer washed well with water (6 × 20 ml). Evaporation of the dried ($MgSO_4$) solvent afforded a gum which consisted almost entirely of the monocarbamate (**6**) (t.l.c. and n.m.r.).

(*c*) The hexahydropyridazine (**4**) (0.200 g, 0.5 mmol) was treated with potassium hydroxide (20 mmol) as in procedure (*b*), but the temperature was held at 150 °C for 4 h. Work-up as before and chromatography on silica gel (benzene–light petroleum as eluant) afforded 8-*methoxy*-5.5-*dimethyl*-5H-*chromeno*[3,4-c]*pyridazine* (**16**) (0.048 g, 36%) as a pale yellow homogeneous (t.l.c.) oil; $\nu_{max.}$(film) 1 620, 1 582, 1 545, and 1 507 cm^{-1}; $\lambda_{max.}$(EtOH) 209 (ε 34 000 dm^3 mol^{-1} cm^{-1}), 221 (39 000), 246sh (11 000), 257sh (10 000), 294 (23 000), and 343nm (32 000); δ ($CDCl_3$) 1.8 (6 H, s), 3.82 (3 H, s), 6.42—6.68 (2 H, m, 7-H + 9-H), 7.43 (1 H, d, *J* 5 Hz, 1-H), 7.55 (1 H, d, *J* 8 Hz,

10-H), and 9.00 (1 H, d, *J* 5 Hz, 2-H) (irradiation at δ 9.00 caused the signal at δ 7.43 to collapse to a singlet) (Found: M^+, 242.1050. $C_{14}H_{14}N_2O_2$ requires *M*, 242.1055).

8-*Methoxy*-3,4,5,5-*tetramethyl*-trans-1,2,3,4,4a,10b-*hexahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**8**).—A solution of the hexahydropyridazine (**4**) (0.200 g, 0.55 mmol) and lithium aluminium hydride (0.038 g, 1.00 mmol) in dry ether (10 ml) was boiled under reflux for 15 min. Ether (10 ml) was added and the organic layer washed with 3M-hydrochloric acid (3 × 20 ml). Neutralisation of the aqueous layer, followed by ether extraction, afforded a solid on evaporation of the dried ($MgSO_4$) solvent. The title compound (**8**) (0.134 g, 88%) was obtained as colourless *prisms*, m.p. 93—94.5 °C (from chloroform–light petroleum); $\nu_{max.}$(KBr) 1 620, 1 585, and 1 505 cm^{-1}; $\lambda_{max.}$(EtOH) 211 (ε 18 000 dm^3 mol^{-1} cm^{-1}), 224sh (7 700), 285 (3 000), and 291 nm (2 800); δ ($CDCl_3$) 1.43 and 1.47 (each 3 H, s, *gem*-Me_2), 1.90—3.27 (6 H, m), 2.42 (6 H, s, 2 × NMe), 3.73 (3 H, s, OMe), 6.32 (1 H, d, *J* 2 Hz), 6.42 (1 H, dd, *J* 2 and 8 Hz), and 7.00 (1 H, d, *J* 8 Hz) (Found: C, 69.5; H, 8.95; N, 10.3%; M^+, 276.1841. $C_{16}H_{24}N_2O_2$ requires C, 69,53; H, 8.75; N, 10.14%; *M*, 176.1838).

3,4-*Bis*(*t-butoxycarbonyl*)-8-*methoxy*-5,5-*dimethyl*-2,3,4,4a-*tetrahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**9**).—To a solution of the diene (**2**; R = H) (0.400 g, 1.84 mmol) in dichloromethane (20 ml) was added di-butyl azodicarboxylate (0.423 g, 1.84 mmol). The solvent was evaporated after 1 h to leave a gum which after column chromatography gave a homogeneous (t.l.c.) mixture of isomers (n.m.r.) of the title compound (**9**) (0.813 g, 99%) as colourless *needles*, m.p. 155 and 157—158 °C (from ethanol); $\nu_{max.}$(KBr) 1 680—1 715, 1 617, 1 580, and 1 505 cm^{-1}; $\lambda_{max.}$(EtOH) 219 (ε 36 000 dm^3 mol^{-1} cm^{-1}), 262 (15 000), 266sh (14 000), 303 (6 900), and 311sh nm (6 860); δ ($CDCl_3$) 1.18 (2.63 H, s, major, 1 × 5-Me), 1.5, 1.60, and 1.62 (total 21 H, 2 × butyl + other 5-Me), 3.77 (4 H, s + m, OMe + 1 × 2-H), 4.30—4.55 (1 H, dd, *J* 12 and 6 Hz, other 2-H), 4.74 (1 H, d, *J* 2 Hz, 4a-H), 6.05—6.28 (1 H, m, 1-H), 6.33—6.65 (2 H, m), and 7.28 (1 H, d, *J* 8 Hz) (irradiation at δ 6.10 caused the signal at 4.74 to collapse to a singlet and that at 4.30—4.55 to collapse to part of an ABq, *J* 12 Hz. Irradiation at δ 4.40 caused the signal at δ 6.05—6.28 to sharpen to a doublet, *J* 2 Hz) (Found: C, 64.7; H, 7.85; N, 6.3%; M^+ 446.2447. $C_{24}H_{34}N_2O_6$ requires C, 64.45; H, 7.75; N, 6.27%; *M*, 446.2417).

3,4-*Bis*(*t-butoxycarbonyl*)-8-*methoxy*-5,5-*dimethyl*-trans-1,2,3,4,4a,10b-*hexahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**10**).—The tetrahydropyridazine (**9**) (0.500 g, 1.12 mmol) was hydrogenated as before. Chromatography gave a homogeneous (t.l.c.) gum (0.472 g, 94%) which gave the title hexahydro derivative as colourless *needles*, m.p. 124—127 °C (from dichloromethane–light petroleum); $\nu_{max.}$(KBr) 1 695, 1 617, 1 580, and 1 505 cm^{-1}; $\lambda_{max.}$(EtOH) 217 (ε 24 000 dm^3 mol^{-1} cm^{-1}), 261 (12 000), 266 (12 000), 303 (6 400), and 310 nm (6 100); δ ($CDCl_3$) 0.9—1.65 (24 H, 5-Me_2 + 2 × butyl), 1.75—2.3 (2 H, m, 1-H_2), 2.95—3.63 (3 H, m, 10b-H + 2-H_2), 3.73 (3 H, s, OMe), 4.29 (major) and 4.26 (minor) (1 H, 2 × d, *J* 8 Hz, 4a-H), 6.23—6.67 (2 H, m), and 7.03 (1 H, d, *J* 8 Hz) (irradiation at δ 3.3 caused the signals at 4.26 and 4.29 to collapse to two singlets, ratio 6:1) (Found C, 64.2; H, 8.3; N, 6.1%; M^+, 448.2608. $C_{24}H_{36}N_2O_6$ requires C, 64.12; H, 8.07; N, 6.23%; M, 448.2573).

8-*Methoxy*-5,5-*dimethyl*-trans-1,2,3,4,4a,10b-*hexahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**7**).—Trifluoroacetic acid (3 ml) was added to the hexahydropyridazine (**10**) (0.100 g, 0.22 mmol) and the solution stirred for 10 min. The solvent was removed under reduced pressure at 40 °C to give the title compound as an initially homogeneous (t.l.c.) *syrup*; δ ($CDCl_3$) 1.20 and 1.48 (each 3 H, s, 2-Me_2), 1.67—3.10 (7 H, saturated H + 2 × NH), 3.48 (1 H, d, *J* 8 Hz, 4a-H), 3.73 (3 H, s, OMe), 6.23—6.62 (2 H, m,), and 7.12 (1 H, d, *J* 8 Hz) (addition of deuterium oxide caused a broad singlet at δ 2.68 to disappear and the remaining signals at 1.67—3.10 to integrate for 5 H) (Found: M^+, 248.1538. $C_{14}H_{20}N_2O_2$ requires *M*, 248.1524).

Atmospheric Oxidation of the Hexahydropyridazine (**7**).—On standing in air at room temperature the hexahydropyridazine (**7**) rapidly darkened and gave a mixture of products (t.l.c.). After 30 min, ^1H n.m.r. spectroscopy revealed that the signal for 4a-H had disappeared and that the amino hydrogen signal now only integrated for 1 H (by difference on treatment with deuterium oxide), but no olefinic signals were observed. Mass spectrometry showed the absence of a significant ion at *m/z* 248 (starting material) but the presence of ions of *m/z* 246 and 244, among others. After 2 h the product was again a mixture but now no exchangeable protons were present (deuterium oxide). After 24 h t.l.c. showed a major product contaminated with several close-running impurities which could not be removed by column chromatography. The ^1H n.m.r. spectrum again showed the absence of exchangeable protons and of olefinic signals and was essentially consistent with the main product being the 1,2-dihydrochromenopyridazine (**19**); δ ($CDCl_3$) 1.47 and 1.55 (2 × 3 H, s), 2.3—2.8 (2 H, m, 1-H_2), 3.2—3.4 (2 H, m, 2-H_2), 3.80 (3 H, s), 6.2—6.7 (2 H, m), and 6.9—7.2 (1 H, d, *J* 8 Hz) (Found: M^+ 244. Calc. for $C_{14}H_{16}N_2O_2$: *M* 244).

7-*Methoxy*-2,2-*dimethyl*-4-(2-*methylprop*-1-*enyl*)-2H-*chromene* (**2**; R = Me).—7-Methoxy-2,2-dimethylchroman-4-one (1.0 g, 4.85 mmol) in dry ether (10 ml) was added under nitrogen to a boiling solution of 2-methylprop-1-enylmagnesium bromide (4.6 g, 29.12 mmol) in dry tetrahydrofuran (7 ml) to which was added ether (7 ml). The mixture was boiled under reflux for 2 h. The cooled reaction mixture was poured onto a mixture of ice and a saturated solution of ammonium chloride. Ether (15 ml) was added and organic material extracted. The ether solution was washed with brine and water, and dried ($MgSO_4$). Removal of the solvent afforded a dark oil (0.78 g) which was purified by silica-gel chromatography (benzene–light petroleum as eluant) to give the title compound (**2**; R = Me) (0.65 g, 55%) as a homogeneous (t.l.c.) *oil*, $\nu_{max.}$(film) 1 615, 1 569, and 1 500 cm^{-1}; δ ($CDCl_3$) 1.37 (6 H, s, *gem*-Me_2), 1.73 and 1.88 (6 H, 2 × s, other *gem*-Me_2), 3.70 (3 H, s, OMe), 5.13 (1 H, s, 3-H), 5.77 (1 H, s, C*H*=CMe_2), 6.23 (1 H, m), and 6.84 (1 H, d, *J* 9 Hz) (Found: M^+, 244.1486. $C_{16}H_{20}O_2$ requires *M*, 244.1463).

8-*Methoxy*-3,4-*bis*(*methoxycarbonyl*)-2,2,5,5-*tetramethyl*-2,3,4,4a-*tetrahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**11**).—A solution of the diene (**2**; R = Me) (0.25 g, 1.02 mmol) in dichloromethane (5 ml) was added to a solution of dimethyl azodicarboxylate (0.13 g, 1.02 mmol) in dichloromethane (5 ml) and the mixture stirred overnight. The solvent was evaporated to leave a gum which solidified on storage at 0 °C. Recrystallisation from chloroform–light petroleum afforded a mixture of two components (*ca.* 2:1 by n.m.r. spectroscopy). An attempt to fractionate the material by silica-gel chromatography was unsuccessful and the products were characterised as a homogeneous (t.l.c.) isomeric mixture of the title compound (**11**) (0.38 g, 95%) as colourless *needles*, m.p. 146—147 °C (from chloroform–light petroleum); $\nu_{max.}$(KBr) 1 705, 1 615, 1 579, and 1 505 cm^{-1}; $\lambda_{max.}$(EtOH) 219 (ε 23 400 dm^3 mol^{-1} cm^{-1}), 259 (16 000), 265 (16 000), 300 (7 400), and 309 nm (6 800); δ ($CDCl_3$) 1.26, 1.46, and 1.65, and 1.77 (12 H, 4 × br s), 3.73 (3 H, s), 3.78 (6 H, s), 4.65 (minor) and 4.85 (major) (total 1 H, 2 × d, *J* 2 Hz, 4a-H), 5.73 (1 H, d, *J* 2 Hz, 1-H), 6.3 (2 H, m), and 7.13 (1 H, d, *J* 8 Hz) (irradiation at δ 5.73 caused the two doublets at 4.6—4.9 to

collapse to singlets) (Found: C, 61.75; H, 6.75; N, 7.35%; M^+ 390.1766. $C_{20}H_{26}N_2O_6$ requires C, 61.51; H, 6.71; N, 7.18%; *M* 390.1791).

8-*Methoxy*-2,2,5,5-*tetramethyl*-3,4-*bis*(*t*-*butoxycarbonyl*)-2,3,4,4a-*tetrahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**13**).—The diene (**2**; R = Me) (0.5 g, 2.05 mmol) in dichloromethane (10 ml) was added to a solution of di-t-butyl azodicarboxylate (0.47 g, 2.05 mmol) in dichloromethane (10 ml) and the mixture stirred overnight. Removal of the solvent and silica-gel chromatography afforded a homogeneous (t.l.c.) isomeric mixture of the title compound (**13**) (0.87 g, 90%) as colourless *needles*, m.p. 150—152 °C (from light petroleum); $\nu_{max.}$(KBr) 1 730, 1 710, 1 617, 1 578, and 1 504 cm^{-1}; $\lambda_{max.}$(EtOH) 218 (ε 26 100 dm^3 mol^{-1} cm^{-1}), 255 (16 600), 264 (16 600), 300 (7 350), and 310 nm (6 640); δ ($CDCl_3$) 1.16 and 1.36 (6 H, 2 × s), 1.46—1.68 (24 H, 2 × Bu^t + other *gem*-Me_2), 3.71 (3 H, s), 3.65 (minor) and 3.80 (major) (total 1 H, 2 × d, *J* 2 Hz, 4a-H), 5.71 (1 H, d, *J* 2 Hz, 1-H), 6.32 (2 H, m), and 7.16 (1 H, d, *J* 8 Hz) (Found: C, 65.8; H, 8.05; N, 5.95%; M^+, 474.2755. $C_{26}H_{38}N_2O_6$ requires C, 65.77; H, 8.06; N, 5.94%; *M* 474.2730).

8-*Methoxy*-3,4-*bis*(*methoxycarbonyl*)-2,2,5,5-*tetramethyl*-trans-1,2,3,4,4a,10b-*hexahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**12**).—The tetrahydropyridazine (**11**) (0.35 g, 0.897 mmol) in ethanol (20 ml) was hydrogenated as before to give, after chromatography, the title material (**12**) as a homogeneous (t.l.c.) mixture of isomers (0.31 g, 90%) as colourless *needles*, m.p. 152—153 °C (major) and 163—164 °C (minor) (from ethanol); $\nu_{max.}$(KBr) 1 700, 1 620, 1 588, and 1 505 cm^{-1}; $\lambda_{max.}$(EtOH) 211 (ε 19 000 dm^3 mol^{-1} cm^{-1}), 283 (4 700), and 289 nm (4 300); δ ($CDCl_3$) 0.76—2.20 (14 H, 2 × *gem*-Me_2 + 1-H_2), 3.20—3.6 (1 H, m, 10b-H), 3.6—4.0 (9 H, 3 × OMe), 4.25 (minor) and 4.40 (major) (total 1 H, 2 × d, *J* 8 Hz, 4a-H), 6.43—6.6 (2 H, m), and 6.78 (1 H, d, *J* 8 Hz) (Found: C, 61.25; H, 7.1; N, 7.1%; M^+, 392.1967. $C_{20}H_{28}N_2O_6$ requires C, 61.20; H, 7.19; N, 7.14%; *M*, 392.1947).

7-*Methoxy*-2,2,5,5-*tetramethyl*-3,4-*bis*(*t*-*butoxycarbonyl*)-trans-1,2,3,4,4a,10b-*hexahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**14**).—The tetrahydropyridazine (**13**) (0.45 g, 0.95 mmol) was hydrogenated as before. The title compound (**14**) (0.40 g, 90%) was obtained as a homogeneous isomeric mixture of *needles*, m.p. 118 and 121—122 °C (from light petroleum); $\nu_{max.}$(KBr) 1 692, 1 620, 1 593, and 1 505 cm^{-1}; $\lambda_{max.}$(EtOH) 219 (ε 19 500 dm^3 mol^{-1} cm^{-1}), 228 (13 800), 280 (5 300), 283 (5 800), and 294 nm (5 150); δ ($CDCl_3$) 0.75—1.55 (24 H, 2 × Bu^t + 2 × *gem*-Me_2), 1.8—2.2 (2 H, m, 1-H_2), 3.35—3.60 (1 H, m, 10b-H), 3.68 (3 H, s, OMe), 4.30 (major) and 4.35 (minor) (total 1 H, 2 × d, *J* 8 Hz, 4a-H), 6.33 (2 H, m), and 6.93 (1 H, d, *J* 8 Hz) (irradiation at δ 2.0 caused the signal at 3.35—3.60 to collapse to two doublets, *J* 8 Hz. Irradiation at δ 3.45 caused the signals at 4.3—4.35 to collapse to two singlets and that at 2.0 to simplify to an ABq, *J* 14 Hz, with additional signals due to the minor isomer.) (At 300 MHz the signal at δ 2.0 became two double doublets, one δ 1.83, *J* 14 and 3 Hz, the other δ 2.08, *J* 14 and 4 Hz.) (Found: C, 65.55; H, 8.3; N, 5.9%; M^+, 476.2914. $C_{26}H_{40}N_2O_6$ requires C, 65.49; H, 8.45; N, 5.9%; *M*, 476.2886).

7-*Methoxy*-2,2,5,5-*tetramethyl*-trans-1,2,3,4,4a,10b-*hexahydro*-5H-*chromeno*[3,4-c]*pyridazine* (**15**).—Trifluoroacetic acid (8 ml) was added to the hexahydropyridazine (**14**) (0.3 g, 0.63 mmol) at room temperature and the solution stirred well. Solvent was removed exhaustively under reduced pressure at 40 °C and the resultant gum passed through alumina in dichloromethane to give the title compound (**15**) as a homogeneous (t.l.c.) *gum* (0.15 g, 88%); δ ($CDCl_3$) 0.9—1.65 (14 H, 2 × *gem*-Me_2 + 1-H_2), 2.36 (2 H, br m, NHNH), 3.27 (2 H, m, 4a-H + 10b-H), 3.73 (3 H, s), 6.39—6.58 (2 H, m), and 7.1 (1 H, d, *J* 8 Hz) (addition of deuterium oxide caused the signal at δ 2.36 to disappear) (Found: M^+, 276.1849. $C_{16}H_{24}N_2O_2$ requires *M*, 276,1838).

Oxidation of the Hexahydropyridazine (**15**).—To the hexahydropyridazine (**15**) (0.2 g, 0.72 mmol) in dry benzene (12 ml) was added mercuric oxide (0.16 g, 0.72 mmol) and the mixture boiled under reflux for 3 h. After filtration and removal of the solvent the resultant gum was chromatographed on neutral alumina (light petroleum–dichloromethane as eluant) to give the major product, 7-*methoxy*-2,2,5,5-*tetramethyl*-1,2-*dihydro*-5H-*chromeno*[3,4-c]*pyridazine* (**23**), as a homogeneous (t.l.c.) gum (0.16 g, 80%); δ ($CDCl_3$) 1.24 and 1.50 (2 × 6 H, s, 2 × *gem*-Me_2), 1.70—2.00 (2 H, ABq, *J* 10 Hz, 1-H_2), 3.70 (3 H, s), 6.1—6.6 (2 H, s), and 7.30 (1 H, d, *J* 9 Hz) (addition of deuterium oxide caused no change) [Found: M^+, 272; (M^+ − 15), 257.1281. $C_{16}H_{24}N_2O_2$ requires *M*, 272; (*M* − 15), 257.1290]. A minor product, also obtained as a homogeneous (t.l.c.) gum (0.02 g, 8%), was characterised as 7-*methoxy*-2,2,5,5-*tetramethyl*-2,4a-*dihydro*-5H-*chromeno*[3,4-c]*pyridazine* (**24**); δ ($CDCl_3$) 1.20 and 1.41 (2 × 6 H, s, 2 × *gem*-Me_2), 4.18 (1 H, d, *J* 1.5 Hz, 4a-H), 5.92 (1 H, d, *J* 1.5 Hz, 1-H), 6.2—6.6 (2 H, m), and 7.00 (1 H, d, *J* 9 Hz) (addition of deuterium oxide caused no change) [Found: M^+, 272; (M^+, − 15), 257.1278. $C_{16}H_{24}N_2O_2$ requires *M*, 272; (*M* − 15), 257.1290].

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References

1 Part 3, P. Anastasis and P. E. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1431.
2 B. T. Gillis and R. Weinkam, *J. Org. Chem.*, 1967, **32**, 3321; R. H. Kent and J-P. Anselme, *Can J. Chem.*, 1968, **46**, 2322; J. C. Howard, G. Gever, and P. H. L. Wei, *J. Org. Chem.*, 1963, **28**, 818; W. Nagata and S. Kamata, *J. Chem. Soc. C*, 1970, 540.
3 E. L. Allred and J. C. Hinshaw, *Chem. Commun.*, 1969, 1021; J. A. Berson and S. S. Olin, *J. Am. Chem. Soc.*, 1969, **91**, 777.
4 E. L. Allred, J. C. Hinshaw, and A. L. Johnson, *J. Am. Chem. Soc.*, 1969, **91**, 3382; M. Martin and W. R. Roth, *Chem. Ber.*, 1969, **102**, 811.
5 J. A. Berson, E. W. Petrillo, and P. Bickart, *J. Am. Chem. Soc.*, 1974, **96**, 636; J. A. Berson, S. S. Olin, E. W. Petrillo, and P. Bickart, *Tetrahedron*, 1974, **30**, 1639.
6 R. C. Neuman and E. W. Ertley, *Tetrahedron Lett.*, 1972, 1225.
7 R. Mechoulam, N. K. McCallum, and S. Burstein, *Chem. Rev.*, 1976, **76**, 75.
8 R. Ya Levina, Yu. S. Shabarov, M. G. Kuz'min, N. I. Vasil'ev, S. I. Pokraka, and E. G. Treshchova, *Zh. Obshch. Khim.*, 1959, **29**, 3541; R. Ya Levina, Yu. S. Shabarov, and M. G. Kuz'min, *Zh. Obshch. Khim.*, 1960, **30**, 2469; M. J. Kornet and J. Y. R. Chu, *J. Pharm. Sci.*, 1983, **72**, 94.
9 M. Rink, S. Mehta, and K. Grubowski, *Arch. Pharm.*, 1959, **292**, 225.
10 M. Tishler and B. Stanovnik, *Adv. Heterocycl. Chem.*, 1968, **9**, 305; P. B. Dervan and D. S. Santilli, *J. Am. Chem. Soc.*, 1980, **102**, 3863.
11 Yu. S. Shabarov, R. Ya. Levina, M. G. Kuz'min, N. I. Vasil'ev, and N. A. Damir, *Zh. Obshch. Khim.*, 1960, **30**, 3210; Yu. S. Shabarov, N. I. Vasi'lev, and R. Ya Levina, *Zh. Obshch. Khim.*, 1961, **31**, 248; Yu. S. Shabarov, M. G. Kuz'min, and R. Ya Levina, *Zh. Obshch. Khim.*, 1960, **30**, 2473.
12 K. Heyns and H. Buchholtz, *Chem. Ber.*, 1976, **109**, 3707.
13 T. R. Lynch, F. N. Machlachlan, and Y. K. Siu, *Can. J. Chem.*, 1971, **49**, 1598; C. H. Wang, S. Hsiao, E. Saklav, and S. G. Cohen, *J. Am. Chem. Soc.*, 1957, **79**, 2661; T. Beetz and R. M. Kellog, *J. Am. Chem. Soc.*, 1973, **95**, 7925; T. L. Levek and E. F. Kiefer, *J. Am. Chem. Soc.*, 1976, **98**, 1875.
14 P. de Mayo and M. C. Usselman, *Can. J. Chem.*, 1973, **51**, 1724.
15 E. E. Schweizer and C. M. Kopay, *J. Org. Chem.*, 1972, **37**, 1561.

16 G. Rosseels, *Ing. Chim.*, 1960, **42**, 285.
17 O. Diels, W. Koll, and J. H. Blom, *Liebigs Ann. Chem.*, 1925, **443**, 242; K. Alder, H. Niklaus, R. Aumüller, and B. Olsen, *ibid*, 1954, **585**, 81.
18 J. P. Snyder, *Tetrahedron Lett.*, 1972, 2451; S. F. Nelson and P. J. Hintz, *J. Am. Chem. Soc.*, 1972, **94**, 7108.
19 M. Tisler and B. Stanovnik, *Adv. Heterocycl. Chem.*, 1979, **24**, 444; W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds, Part 1,' J. Wiley, New York, 1977, p. 172; W. E. Stewart and T. H. Siddall, *Chem. Rev.*, 1970, **70**, 536; G. Binsch, *Top. Stereochem.*, 1968, **3**, 98.
20 E. W. Bitner and J. T. Gerig, *J. Am. Chem. Soc.*, 1972, **94**, 913.
21 G. R. Weisman and S. F. Nelson, *J. Am. Chem. Soc.*, 1976, **98**, 7007.
22 H. Booth and D. V. Griffiths, *J. Chem. Soc., Chem. Commun.*, 1973, 666.
23 J. E. Anderson and J. M. Lehn, *Bull. Soc. Chim. Fr.*, 1966, 2402; E. L. Allred, C. L. Anderson, R. Miller, and A. L. Johnson, *Tetrahedron Lett.*, 1967, 525; J. E. Anderson and J. M. Lehn, *J. Am. Chem. Soc.*, 1967, **89**, 81.
24 G. Fraenkel and C. Franconi, *J. Am. Chem. Soc.*, 1960, **82**, 4478; R. J. Gillespie and T. Birchall, *Can. J. Chem.*, 1963, **43**, 148; S. J. Kuhn and J. S. McIntyre, *Can. J. Chem.*, 1965, **43**, 995.
25 L. M. Jackman, T. E. Kavanagh, and R. C. Haddon, *Org. Magn. Reson.*, 1969, **1**, 109.
26 B. C. Challis, J. N. Iley, and H. S. Rzepa, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1037.
27 P. J. Battye, J. F. Cassidy, and R. B. Moody, *J. Chem. Soc., Chem. Commun.*, 1981, 68.
28 R. Glaser, S. Geresh, and V. Schöllkopf, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1746.
29 K. Umemoto and K. Ouchi, *Org. Magn. Reson.*, 1981, **15**, 13; F. Bernardi, L. Lunazzi, and P. Zanirato, *Tetrahedron*, 1977, **33**, 1337.
30 N. Korberg and D. Kost, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1661.
31 R. M. Moriarty, M. R. Murphy, S. J. Druck, and L. May, *Tetrahedron Lett.*, 1967, 1603.
32 H. A. Staab and D. Lauer, *Tetrahedron Lett.*, 1966, 4593.
33 A. Cipiciani, P. Linda, D. Macciantelli, and L. Lunazzi, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1045.
34 A. Dondoni, L. Lunazzi, P. Zanirato, and G. Cerioni, *J. Chem. Soc., Perkin Trans. 2*, 1980, 717.
35 O. Dann, K. W. Hagedorn, and H. Hofmann, *Chem. Ber.*, 1971, **104**, 3313.

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