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

CONFIGURATIONAL STUDIES WITH DERIVATIVES OF PERHYDRO-OXAZOLO[3,4-*c*]OXAZOLE AND THE CONFORMATIONAL ANALYSIS OF PERHYDRO-IMIDAZO[1,5-*c*]THIAZOLE

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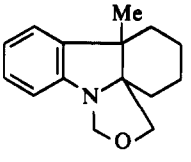
Abstract—A series of 3-monosubstituted, 3,3'-disubstituted, and 3,5-disubstituted perhydro-7a-methyloxazolo[3,4-*c*]oxazoles has been synthesised. Some indication of the predominant conformations of these systems and of the related perhydro-imidazo[1,5-*c*]thiazoles is obtainable from the magnitude of the geminal coupling constants of the methylene group protons situated between the heteroatoms.

The most negative geminal coupling constants (J_{gem}) for the methylene group protons situated between a N and an O atom in a 5-membered ring have been observed[2] for the oxazolo-indole derivatives (**1** and **2**) where values of −7 Hz and −6 Hz have been recorded. This deviation from the range of values (−3·0 to −5·0 Hz) usually observed[3,4] for the C(2)-protons in a number of simply substituted oxazolidines may be a natural consequence of the predominant conformations adopted by a system possessing two fused 5-membered rings, together with an effect arising from delocalization of the nitrogen lone pair over the aromatic ring. As part of an investigation aimed at evaluating the relative importance of these two factors and of studying the stereochemistry of saturated 5-membered ring heterocyclic systems it was decided to examine the NMR spectra of systems (**3**, **4**, and **5**) and of some simple monocyclic oxazolidines (**6**). In addition, to extend the results obtained on the systems (**3**, **4** and **5**) the perhydroimidazo[1,5-*c*]thiazole system (**7**) was selected.

Synthesis of compounds. The 3,5-disubstituted compounds (**3**; R' or R'' = H) were prepared from 2-amino-2-methyl-1,3-propanediol by reaction with two molar equivalents of the appropriate aldehyde and the compounds (**4**) from the same aminodiol by reaction with one molar equivalent of an aldehyde or ketone followed by one molar equivalent of formaldehyde (Scheme 1). Mixtures of *cis*- and *trans*-(3-H,5-H)-isomers of (**3**; R' or R'' = H) were obtained using aryl aldehydes and these were separated by fractional crystallisation. Previously only one isomer of 3,5-diphenylperhydro-7a-methyloxazolo[3,4-*c*]oxazole had been described.[5] In some cases also (Exerpimental) it was possible by fractional crystallisation to obtain both isomers of (**4**; R,R' = H, Aryl). A mixture of isomeric 2-amino-1-phenyl-1,3-propanediols prepared as described in the literature[6] was condensed with formaldehyde and the isomers of **5** so obtained



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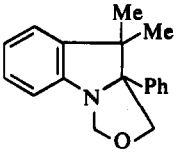

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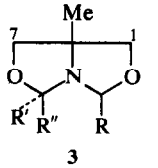

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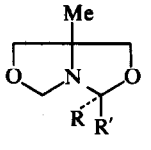

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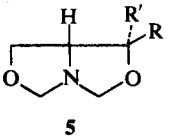

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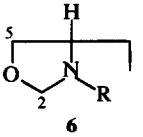

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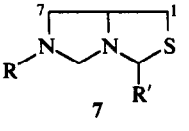

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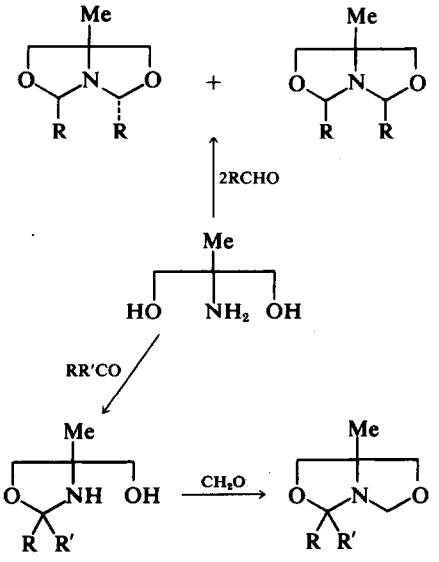
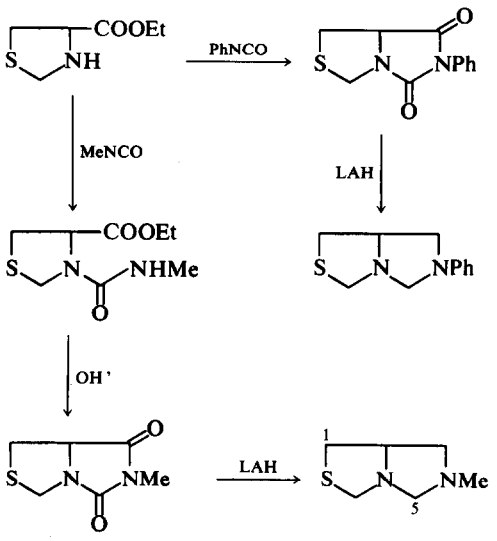


SCHEME 1. Syntheses of perhydro-7a-methyloxazolo[3,4-*c*]oxazoles.



SCHEME 2. Syntheses of perhydro-6-phenyl- and perhydro-6-methylimidazo[1,5-*c*]thiazoles.

were separated by column chromatography. The oxazolidines (**6**) were prepared by formaldehyde treatment of the products of reductive alkylation of various substituted 1,3-aminoalcohols.

The synthesis of perhydro-6-phenylimidazo[1,5-*c*]thiazole (**7**; R′ = H, R = Ph) was carried out as shown in Scheme 2. L-Thiazolidine-4-carboxylic acid was esterified and the N-phenylhydantoin prepared from the ester by treatment with phenyl isocyanate. The hydantoin was reduced with LAH to give the required perhydroimidazo[1,5-*c*]-thiazole. Reduction of the phenyl hydantoin with LAD gave the corresponding 5,5,7,7-tetradeuterio compound.

When the ethyl ester of thiazolidine-4-carboxylic acid was reacted with a slight excess of methyl isocyanate, the yellow syrup which resulted was not the N-methylhydantoin, but the N-carbamoyl derivative (Scheme 2). This is similar to the reaction between proline ester and methyl isocyanate.[7] In this case, ring closure was effected by refluxing with a small amount of ethanolic potassium hydroxide. This method was employed successfully in the present case to give the hydantoin which was reduced to perhydro-6-methylimidazo[1,5-*c*]thiazole (**7**; R′ = H, R = Me).

2-Methylthiazolidine-4-carboxylic acid ethyl ester hydrochloride was prepared by condensing L-cysteine ethyl ester hydrochloride with paraldehyde in the presence of a trace of hydrogen chloride.[8] The free amine was obtained by treatment with potassium carbonate and the N-phenylhydantoin prepared from this. Reduction as before yielded perhydro-3-methyl-6-phenylimidazo[1,5-*c*]thiazole (**7**; R = Ph, R′ = Me).

RESULTS AND DISCUSSION

(a) *Perhydro-7-methyl-oxazolo*[3,4-c]*oxazole and its* 3,3-*disubstituted derivatives.* An examination of Dreiding models shows that **4** (R = R′ = H) can exist in a number of rather flexible *cis*-fused conformations and as in the case of the related hexahydropyrrolizine system[9] the models indicate that partial pseudorotation occurs in each ring. Models of the *trans*-fused conformations are not as flexible and are certainly strained, but the ready deformability of tertiary nitrogen may reduce this in the actual molecule. In addition the presence of the O atoms in the rings may also facilitate *trans*-fusion since although *trans*-bicyclo[3.3.0]octane is considerably strained[10] the 3-oxa-derivatives[11] appear to be relatively less unstable in the *trans* conformation. Thus both *cis* and *trans* conformations, interconvertible by inversion of the nitrogen atom, are possible for **4** (R = R′ = H) but since hexahydropyrrolizine[9] exists in the *cis*-fused form over the temperature range − 70 to + 190° this is the expected predominant ring fusion for **4** (R = R′ = H).

The undistorted model of the *cis*-fused conformation shows the presence of two unfavourable non-bonded interactions between the C(3)-H and C(5)-H bonds, and between the C(1)-H and C(7)-H bonds (distance of approach *ca* 1·7 Å which is considerably less than the combined van der Waals radii of two hydrogens (2·4 Å)). Thus this conformation may be ignored. If it were present to any appreciable extent it would be characterised by a J_{gem} (C(3)-methylene) of *ca* − 1 Hz (oxygen and nitrogen lone pair eclipsing adjacent CH bonds)[12,13] instead of the observed (benzene solution) J_{gem} of − 6 Hz. The situation which best accords with the NMR evidence and with (in models) a minimization

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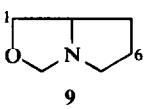

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of non-bonded interactions appears to involve a rapid equilibrium between conformations such as **8**. In the *exo*-buckled ring A the nitrogen lone pair is near *trans* and axial with respect to an adjacent CH and in an *endo* ring the same CH approaches a skew relationship. Both of these lone pair —CH relationships would give rise to rather negative J_{gem} values. A similar conformational equilibrium has been proposed for certain pyrrolizidine alkaloids.[14] For comparison purposes the NMR spectrum of perhydropyrrolo[1,2-*c*]oxazole (**9**) was examined and J_{gem} for the C(3) methylene protons found to be $-6{\cdot}0$ Hz, a very similar J_{gem} to that observed for the corresponding protons in **4** (R = R′ = H). As in the case of hexahydropyrrolizine[9] the NMR spectrum of **4** (R = R′ = H) did not change appreciably over the range $-85°$ to 110°, suggesting the absence of a *cis*-fused⇌*trans*-fused equilibrium.

Complete details concerning the NMR spectrum of **4** (R = R′ = H) and of its 3,3′-disubstituted derivatives are summarised in Table 1. As may be seen, J_{gem} for the C(3)–(C(5)-) methylene protons is even more negative than in the parent compound and the J_{gem} of $-8{\cdot}0$ Hz recorded for **4** (R = R′ = Me) is the most negative yet recorded for NCH_2O protons situated in a 5-membered ring. In the case of the 3,3′-disubstituted derivatives the one compound which deviates from near uniformity of spectral data is the spirocyclopentano-compound in which J_{gem} ($-6{\cdot}4$ Hz) is closer to that of the parent compound (-6 Hz) rather than that ($-7{\cdot}5$ to $-7{\cdot}8$ Hz) of the other compounds in Table 1. Examination of the unstrained Dreiding model of **4** (R = spirocyclopentyl) with that for example of **4** (R = spirocyclohexyl) shows a much closer approach of one of the cyclopentyl CH bonds to the pseudoaxial C(5)-H bond than occurs in the spirocyclohexyl compound. Although it is not expected for either compound to exist in this conformation nevertheless this study of the model suggests that the change in J_{gem} is consequent upon changes in non-bonded interactions which in turn influence the position of conformational equilibrium.

(b) 3,5-*Disubstituted perhydro-7a-methyloxazolo*[3,4-c]*oxazoles.* Both diastereoisomers of the 3,5-diaryl compounds were obtained by the condensation of the amino diol with two molecular equivalents of the arylaldehyde. The configurations of these were readily assigned from the NMR spectral data (Table 2). Thus in the case of the 3,5-diphenyl compounds the major isomer showed a two proton singlet at δ 5·47 (CCl_4) for the C(3)- and C(5)-protons and a four proton quartet δ 3·74 and 3·62 ($J = -8{\cdot}4$ Hz) for the C(1)- and C(7)-protons. This identity of chemical shifts of the C(3)- and C(5)-protons and of the C(1)-methylene pair with the C(7)-methylene pair implies the symmetrical *cis*-(3-H,5-H)-configuration. Dreiding models for the *cis* isomer suggest a *cis* conformation undergoing partial pseudorotation to relieve unfavourable C(3)- and C(5)-interactions.

The *trans*-(3-H,5-H)-isomer showed two singlets for the C(3)- and C(5)-protons consistent with its unsymmetrical structure. In all cases J_{gem} for the C(7)- and C(1)-methylene protons varied only between $-8{\cdot}3$ to $-8{\cdot}8$ Hz, values only slightly more negative than those recorded for the C(7)-methylene protons in the compounds listed in Table 1.

(c) 3-*Monosubstituted perhydro-7a-methyloxazolo*[3,4-c]*oxazoles.* The NMR data on these compounds is summarised in Table 3. As can be seen, two isomers of the 3-*p*-nitrophenyl compound were obtained, the major isomer, m.p.

Table 1. NMR spectra (60 MHz) of 3,3′-disubstituted perhydro-7a-methyloxazolo[3,4-*c*]oxazoles

Compound	Solvent	H_5	$H_{5'}$	$J_{5,5'}$	H_7	$H_{7'}$	$J_{7,7'}$	H_1	$H_{1'}$	$J_{1,1'}$	Me_{7a}
4, R = R′ = H	C_6H_6	4·28	4·18	−6·0	3·50	3·21	−8·0	3·50	3·21	−8·0	0·99
4, R = R′ = Me	C_6H_6	4·60	4·08	−7·8	3·58		—	3·48	3·12	−8·0	1·05
	CCl_4	4·61	4·06	−8·0	3·70		—	3·55	3·25	−8·0	1·31
	CD_3CN	4·69	4·09	−7·8	3·75		—	3·58	3·27	−8·0	1·35
4, R = R′ = Et	C_6H_6	4·58	4·10	−7·8	3·50		—	3·44	3·10	−8·0	1·04
	CCl_4	4·58	4·10	−7·8	3·62		—	3·50	3·22	−8·0	1·22
	CD_3CN	4·67	4·11	−7·8	3·69		—	3·58	3·26	−8·0	1·21
4, R = R′ =	C_6H_6	4·56	4·22	−6·6	3·49	3·42	−8·8	3·47	3·26	−8·2	1·07
spirocyclopentyl-	CCl_4	4·51	4·18	−6·4	3·63	3·56	−8·8	3·58	3·36	−8·2	1·25
	CD_3CN	4·61	4·20	−6·4	3·69	3·62	−8·8	3·64	3·38	−8·2	1·24
4, R = R′ =	C_6H_6	4·70	4·10	−7·7	3·53		—	3·46	3·17	−7·8	1·06
spirocyclohexyl-	CCl_4	4·67	4·03	−7·6	3·66		—	3·50	3·23	−7·8	1·22
	CD_3CN	4·76	4·07	−7·8	3·75	3·70	—	3·56	3·28	−7·8	1·23
4, R = R′ =	C_6H_6	4·70	4·09	−7·8	3·50		—	3·45	3·12	−8·0	1·04
4-t-butylspiro-	CCl_4	4·65	4·03	−7·8	3·68		—	3·50	3·21	−7·8	1·22
	CD_3CN	4·74	4·04	−7·8	3·72		—	3·55	3·25	−8·0	1·22

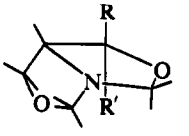
Table 2. NMR spectra of 3,5-disubstituted-perhydro-7a-methyloxazolo[3,4-*c*]oxazoles

Compound	Solvent	H_3	H_5	H_1	$H_{1'}$	$J_{11'}$	H_7	$H_{7'}$	$J_{77'}$	Me_{7a}
(3; R = R″ = phenyl, R′ = H)	CCl_4	5·47		3·74	3·62	−8·4	3·74	3·62	−8·4	1·2
	C_6H_6	5·52		3·54	3·46	−8·5	3·54	3·46	−8·5	1·0
(3; R = R′ = phenyl, R″ = H)	CCl_4	5·53	5·12	3·96	3·54	−8·4	3·62		—	1·4
	C_6H_6	5·57	5·54	3·77	3·28	−8·5	3·57		—	1·1
(3; R = R″ = *p*Clphenyl, R′ = H)	CCl_4	5·40		3·73	3·61	−8·5	3·73	3·71	−8·5	1·2
	C_6H_6	5·27		3·46	3·36	−8·5	3·46	3·36	−8·5	0·9
(3; R = R′ = *p*Clphenyl, R″ = H)	CCl_4	5·47	5·05	3·97	3·55	−8·3	3·72		—	1·4
	C_6H_6	5·30	5·20	3·66	3·22	−8·4	3·46		—	1·0
(3; R = R″ = *p*NO_2phenyl, R′ = H)	$CDCl_3$	5·71		4·01	3·79	−8·6	4·01	3·79	−8·6	1·3
	C_6H_6	5·13		3·49	3·25	−8·4	3·49	3·25	−8·4	0·82
	Pyridine	5·92		3·97	3·74	−8·6	3·97	3·74	−8·6	1·2
(3; R = R′ = *p*NO_2phenyl, R″ = H)	$CDCl_3$	5·69	5·10	4·16	3·70	−8·8	3·99	3·79	−8·8	1·5
	Pyridine	5·77	5·39	4·18	3·68	−8·7	4·00	3·84	−8·8	1·4

88–90°, showing an AB quartet for the C(5)-methylene protons with J_{gem} −6·8 Hz. The minor isomer, m.p. 128–130°, showed a singlet for the C(5)-methylene protons but use of the chemical shift reagent Eu(fod)$_3$ enabled the coupling constant between the C(5)-methylene protons to be determined as −6·4 Hz. This coupling constant was assumed to be close to that in the spectrum of the uncomplexed material since the other coupling constants in this spectrum were not significantly altered by the addition of Eu(fod)$_3$. By means of the same reagent the J_{gem} (−8·1 Hz) between the C(7)-methylene protons of the major isomer was also obtained. Examination of Dreiding models suggests that **4** (R = H, R′ = *p*-nitrophenyl) should be thermodynamically more stable than **4** (R′ = H, R = *p*-nitrophenyl) since in the latter case the bulky aryl substituent is in the *endo*-position. Thus the *exo*-substituted stereochemistry could be tentatively assigned to the major isomer, m.p. 88–90°. In support of this the minor isomer was found to be completely converted to the more stable major isomer on treatment with a small amount of acid in ethanol. Similar treatment of the major isomer resulted in no observable change. Additional evidence for the *endo*-substituted structure **4** (R′ = H, R = *p*-nitrophenyl) for the minor isomer was long-range coupling (*ca* 1·1 Hz) between one of the C(1)- and one of the C(7)-protons. Examination of Dreiding models of this compound constrained so that the aryl substituent adopts a nearly pseudoequatorial position results in an almost planar W stereochemistry between H(7)-C—C—C-H(1) where the protons in question are those *cis* to the angular Me group.

Three other 3-aryl substituted compounds were prepared but in each case only one isomer was isolated. For each compound the spectrum obtained was similar to that of the (*trans* 3-H,7a-Me)-3-*p*-nitrophenyl isomer indicating the same stereochemistry for all four compounds.

Similarly, only one isomer of each of the three



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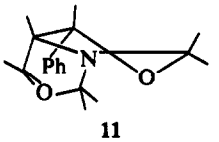

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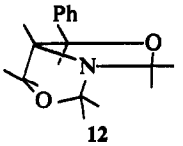

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alkyl substituted compounds was obtained in a pure state and these were assigned the stereochemistry (**4**; R = H, R′ = alkyl) since not only is this the stereochemistry of the more stable isomer but because the general appearance of the NMR spectrum of each of these compounds is similar to that of the (*trans*-3H,7a-Me)-3-*p*-nitrophenyl compound.

(d) *Perhydro-1-phenyloxazolo*[3,4-c]*oxazoles* (**5**). Examination of unstrained Dreiding models (**10**) of the two diastereoisomeric perhydro-1-phenyl-oxazolo[3,4-*c*]oxazoles (**5**) shows the phenyl substituent to be *endo* in the *cis*(1-H,7a-H) isomer (**10**; R′ = Ph, R = H) and *exo* in the *trans*(1-H,7a-H) isomer (**10**; R = Ph, R′ = H). In order to minimise non-bonded interactions both isomers will adopt conformations possessing a *pseudo*-equatorial phenyl substituent and, in models, this is achieved by pinching together either the *exo* hydrogens on C(1) and C(3) in the case of the *cis*(1-H,8a-H) isomer, or the corresponding *endo* hydrogens in the *trans*(1-H,7a-H) isomer; in both cases the conformation of the unsubstituted ring may remain largely unaffected. In these conformations (**11** and **12**) the degree of overlap of the C(3) methylene group with the adjacent nitrogen lone pairs varies, whereas overlap with the oxygen lone pairs is approximately the same. In the conformation **11** of the *cis*(1-H,7a-H) compound the nitrogen lone pair approxi-

Table 3. NMR spectra of 3-monosubstituted-perhydro-7a-methyloxazolo[3,4-*c*]oxazoles

Compound	Solvent	H_3	H_5	$H_{5'}$	$J_{55'}$	H_1	$H_{1'}$	$J_{11'}$	H_7	$H_{7'}$	$J_{77'}$	Me_{7a}
(4; R = H, R′ = Et)	CCl_4	4·11	4·34	4·18	−7·0	3·84	3·48	−8·2	3·70	3·20	−8·6	1·22
(4; R = H, R′ = iPr)	CCl_4	4·99	4·37	4·20	−7·0	3·82	3·48	−8·0	3·72	3·22	−8·2	1·28
(4; R = H, R′ = tBu)	CCl_4	4·89	4·34	4·19	−6·6	3·84	3·43	−8·0	3·70	3·20	−7·6	1·20
(4; R = H, R′ = phenyl)	CCl_4	5·20	4·44	4·24	−6·8	3·83	3·28	−8·4	3·75	3·65	−8·4	1·22
(4; R = H, R′ = *p*Clphenyl)	CCl_4	5·18	4·47	4·25	−6·8	3·80	3·30	−8·4	3·83	3·68	−8·4	1·25
(4; R = H, R′ = *p*MeOphenyl)	CCl_4	5·05	4·38	4·16	−6·7	3·78	3·23	−8·4	3·69	3·62	−8·4	1·23
(4; R = H, R′ = *p*NO_2phenyl)	$CDCl_3$	5·33	4·54	4·33	−6·8	3·89	3·40	−8·3	3·82		−8·1	1·30
	C_6H_6	5·04	4·23	4·13	−6·9	3·52	3·08	−8·8	3·46		—	0·94
	Pyridine	5·50	4·71	4·40	−6·6	3·94	3·41	−8·4	3·86		—	1·27
(4; R = *p*NO_2phenyl, R′ = H)	$CDCl_3$	5·58	4·08		−6·4	3·92	3·64	−8·4	4·10	3·69	−8·5	1·42
	C_6H_6	5·21	3·98		—	3·54	3·23	−8·5	3·68	3·29	−8·5	1·02
	Pyridine	5·61	4·17		—	3·96	3·61	−8·4	4·10	3·61	−8·6	1·33

Table 4. NMR spectra of perhydro-1-phenyloxazolo[3,4-*c*]oxazoles

Compound	Solvent	Operating frequency (MHz)	H_3	$H_{3'}$	$J_{3,3'}$	H_5	$H_{5'}$	$J_{5,5'}$	H_1	$J_{1,(7a)}$	H_7	$H_{7'}$	$J_{7,7'}$	$J_{7,(7a)}$	$J_{7',(7a)}$	$H_{(7a)}$
(5; R = H, R′ = Ph)	C_6H_6	60	4·36	4·36	—	4·17	4·17	s	4·72	5·9	3·05					3·70
	$CDCl_3$	60	4·75	4·60	−6·3	4·63	4·42	−5·7	5·04	6·0	3·33	3·33	—	5·0	5·0	3·88
(5; R = Ph, R′ = H)	C_6H_6	220	4·74	4·21	−4·3	4·20	4·11	−5·9	4·40	5·8						
	CCl_4	220	4·76	4·32	−4·0	4·38	4·18	−6·0	4·37	6·2	3·88	3·63	−9·0	1·3	5·8	3·38
	$CDCl_3$	60	4·90	4·47	−4·1	4·55	4·23	−5·9	4·55	5·5	4·04	3·73	−8·1	1·6	5·5	3·58

mately bisects the C(3) methylene group whereas in the conformation **12** of the *trans*(1-H,7a-H) compound the lone pair is more nearly *trans* coplanar with one of the C(3)-H bonds. Hence one expects[15] a more positive value of J_{gem} between the C(3) methylene protons in the case of the *trans*(1-H, 7a-H) isomer and this is in fact observed (−4·1 Hz compared with −6·3 Hz for the corresponding J_{gem} in the *cis*(1-H, 7a-H) isomer—Table 4).

Further evidence for these conformations is given by the value of the vicinal coupling constants $J_{1,7a}$. In the undistorted model (**10**) dihedral angles of *ca* 0° and *ca* 120° exist between the 1-H and 7a-H protons in the *endo* and *exo* substituted isomers respectively, corresponding[16] to values of $J_{1,7a}$ of *ca* 8 and *ca* 2 Hz, compared with the observed values of 6·0 and 5·6 Hz. In the case of the conformations (**11** and **12**) however, the corresponding dihedral angles are closer to 30° and 150° respectively which would result in values of $J_{1,7a}$ of similar magnitude (*ca* 6 Hz).

The suggestion that the unsubstituted ring possesses a very similar conformation in both isomers is supported by the similar values of $J_{5,5'}$ (− 5·7 Hz in the *cis*(1-H,7a-H) isomer and − 5·8 Hz in the *trans*(1-H,7a-H) isomer) which shows that the degrees of overlap of the C(5) methylene protons with the adjacent lone pairs are almost identical.

(e) *Monocyclic perhydro-oxazoles.* In part to mimic the structure of the bicyclic compounds (**3, 4** and **5**), a series of 3-substituted-4-ethyl-oxazolidines (**6**) were prepared and their NMR spectra summarised in Table 5.

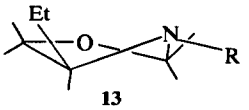
The conformational analysis of 5-membered ring fully reduced heterocycles is complicated by their low barriers to pseudorotation, so that the spectral data represents an average of a large number of conformations. However, the decrease in the magnitude of J_{gem} (C(2)-methylene protons) with increasing size of the 3-substituent would appear to be a result of a shift in the average conformation, and this is supported by the corresponding variation in value of one of the $J_{4,5}$ vicinal coupling constants.

One important contributor to **6** (R = Me) is expected to be **13** since here eclipsing between H-4 and H-5 is minimised and both the N-Me group and the Et group occupy pseudoequatorial positions. Measurements on the model of this conformation show dihedral angles between H-4 and both H-5 bonds of *ca* 30° and 150° which should result in two vicinal coupling constants of *ca* 6 Hz. Reference to Table 5 shows experimental results (J = 6·9 and 6·4 Hz) in agreement with expectations.

As the N-substituent increases in size, the steric repulsion between the C(4)-Et group and the N-substituent in conformation **13** becomes greater and to minimise this the protons on C(4) and C(5) approach more closely an eclipsed arrangement (dihedral angles approaching *ca* 0° and 120°). This change should be paralleled by an increase in magnitude of $J_{4,5}$ (*cis*), and a decrease in $J_{4,5}$ (*trans*). The former trend is expected to be of smaller magnitude than the latter, due to the difference in shape of the Karplus curve[16] over the different ranges. In fact the change in $J_{4,5}$ (*cis*) is not marked and $J_{4,5}$ (*trans*) changes from 6·4 to 4·4 Hz.

Thus a correlation can now be made between average conformations of **6** and J_{gem} (C(2)-methylene) in that the more nearly eclipsing the geometry at C(4) and C(5) the more negative the coupling constant. This is reasonable since a conformation such as **13** in which the dihedral angles between the C(4) and C(5) protons are *ca* 30° and 150° a near eclipsing of lone pair orbitals with the C(2)-H bonds would be likely resulting in a rather large value of J_{gem} whereas in for example (**14**) a more staggered arrangement of lone pairs and C(2)-H bonds will be present resulting in a small value of J_{gem}. These arguments of course refer to predominant conformations in a rapidly pseudorotating set of conformations but nevertheless satisfactorily rationalise the spectra data.

(f) *6-Substituted perhydroimidazo*[1,5-c]*thiazoles.* Unlike the perhydro-oxazolo[3,4-*c*]oxazole system, where very negative values of J_{gem} for the methylene group situated between the heteroatoms were encountered, the spectra of the perhydro-imidazothiazoles (Table 6) show a very



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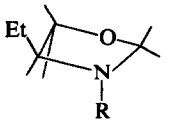

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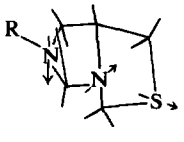
Table 5. NMR spectra of 3-substituted-4-ethyl-oxazolidines (**6**)

Compound	Coupling Constants (Hz)				Chemical Shifts (δ)				
	$J_{2,2'}$	$J_{5,5'}$	$J_{4,5}$	$J_{4,5'}$	H_2	$H_{2'}$	H_5	$H_{5'}$	H_4
(**6**; R = Me)	−4·3	−7·3	6·9	6·4	4·39	3·98	3·86	3·29	2·32
(**6**; R = Et)	−5·4	−7·8	7·8	5·4	4·37	4·12	3·81	3·20	*ca* 2·45
(**6**; R = i-Pr)	−5·9	−7·5	7·5	4·8	4·41	4·21	3·77	3·18	*ca* 2·75
(**6**; R = cyclohexyl)	−5·9	−7·6	6·9	4·5	4·43	4·23	3·77	3·20	2·79
(**6**; R = benzyl)	−5·3	−7·7	6·8	5·3	4·30	4·18	3·89	3·23	2·60
(**6**; R = α-methylbenzyl)	−6·0	−7·8	6·8	4·4	4·30	4·11	3·70	3·21	2·80

large value of J_{gem} (− 3·7 Hz) for the C(5)-methylene protons and a small J_{gem} (− 10·0 Hz) for the C(3)-methylene protons. Examination of Dreiding models, constructed such that the distance between the C(3)- and C(5)-*endo* hydrogens is as great as possible (*ca* 2·2 Å), shows the necessity of considering the two conformations (**15** and **16**). In **15**, the N—C(3) bond is pseudoaxial with respect to the imidazole ring and in **16** this bond is pseudoequatorial. In **15** the dihedral angle between the bridgehead nitrogen lone pair and the C(5) pseudoequatorial proton is *ca* 90°, whereas in **16** the corresponding angle is *ca* 30°. Reference to the J_{gem}-dihedral angle relationship for N—CH_2 systems[15] shows that **16** would be characterised by a large J_{gem} for the C(5)-methylene group and in fact the imidazolidine ring geometry of **16** resembles closely that in 2-phenylperhydroimidazo[1,5-*a*]pyridine (**17**)[17] which shows an identical value of J_{gem} for the C(3)-methylene group (− 3·8 Hz) to that in **7** (R′ = H, R = Ph). In a similar way, the J_{gem} value for the C(3)-methylene protons should be larger in **15** than in **16**, the dihedral angle between the bridgehead nitrogen lone pair and the pseudoequatorial proton being *ca* 30° and 90° respectively, and the observed J_{gem} of − 10·0 Hz suggests conformation **16**. Further conformational information is given by the vicinal couplings between the C(1)-methylene group and the C(7a)-angular proton. In order for such couplings to be of similar magnitudes (*ca* 6·7 and 7·8 Hz) the relevant dihedral angles must be *ca* 30° and 150°. Study of Dreiding models shows that these angles are readily accommodated by **16** but not by conformation **15**.

Thus the evidence supports **16** as the predominant conformation of the 6-substituted-perhydroimidazo[1,5-*c*]thiazoles. This is explicable in terms of a minimisation of dipolar interaction involving the heteroatoms, for it is by the adoption of conformation (**16**) that the unfavourable resultant dipolar forces which exist between the bridgehead N and the S atom in the alternative conformation **15** can be avoided. The presence of the long C—S bonds in **7** must be responsible for its existence in predominantly one conformation. In fact models of **7** fall readily into conformations **15** and **16** and these are interconvertible by a partial ring inversion and the conformational arguments used for this system are similar to those used for **17**, as a consequence of the almost isosteric thiazolidine and piperidine rings. Compounds **4** in which both rings are "small" (short C—O and C—N bond lengths) do not naturally fall into such clearly defined conformations and are not amenable to such a simple conformational treatment.



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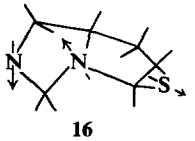

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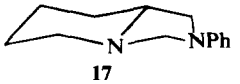

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EXPERIMENTAL

Elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, Germany, and also by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic. IR spectra were recorded on a Perkin-Elmer 457 grating instrument as 0·2 M solutions using 0·2 mm matched cells. The NMR spectra were determined on a Perkin-Elmer R10, Varian T60 and Varian HR-220 MHz spectrometers as 10% solns with TMS as internal reference.

General procedure for preparation of 3,3-*disubstituted-perhydro-*7a-*methyloxazolo*[3,4-c]*oxazoles.* The appropriate ketone (0·25 M) was added to a mixture of 2-amino-2-methyl-1,3-propanediol (0·25 M) and absolute benzene (125 ml) contained in a 250 ml flask fitted with a Dean and Stark apparatus. The mixture was refluxed (1 to 6 hr) until the theoretical amount of water (0·25 M) had been collected. The benzene was then removed *in vacuo*, a slight excess of 36% formaldehyde added to the syrupy residue and the mixture shaken vigorously for 15 min, when two layers separated. The upper organic layer was extracted with ether, and the combined extracts washed once with brine, dried (Na_2SO_4), the ether evaporated and the residual oil distilled under reduced pressure. The experimental results are summarised in Table 7.

General procedure for preparation of 3-*substituted-perhydro-*7a-*methyloxazolo*[3,4-c]*oxazoles.* These compounds were prepared by the method described above except that aldehydes (0·25 M) were used in place of ketones. The reaction of the aminodiol with the aldehydes was much faster and the water removal took a maximum of 3 hr. The products from these preparations were assumed to be mixtures of the *cis* and *trans* isomers, but in all but one case only one isomer was obtained. The experimental results are shown in Table 7.

cis *and* trans-(3-H,7a-Me)*Perhydro-*3-p-*nitrophenyl-*7a-*methyloxazolo*[3,4-c]*oxazole.* The NMR spectrum of the crude product showed a ratio of isomers of approximately 3:2. The minor isomer was deposited first in a fractional recrystallisation from ether–chloroform and obtained in a pure state after one further crystallisation as fine pale yellow needles, m.p. 128–130°. The major isomer was deposited second from ether–chloroform and was obtained pure after three further recrystallisations as fine pale yellow needles, m.p. 88–90°, which were light sensitive, becoming bright yellow-green and powdery over a period of days in sunlight. The experimental results are shown in Table 7.

Equilibration of cis and trans-(3-H,7a-Me)*perhydro-*3-p-*nitrophenyl-*7a-*methyloxazolo*[3,4-c]*oxazole.* A pure sample of each isomer (1 g) was added in separate experiments to EtOH (20 ml) to which conc HCl (5 drops) was added. The mixture was stirred for 4 weeks. The EtOH and water traces were removed *in vacuo* yielding a yellow powder in each case. The NMR spectra of the two samples were now found to be identical and superimposable upon a spectrum of the pure major isomer. Recrystallisa-

Table 6. NMR spectra of perhydro-imidazo[3,4-*c*]thiazoles

Compound	Solvent	H_3	$H_{3'}$	$J_{3,3'}$	H_5	$H_{5'}$	$J_{5,5'}$	H_1	$H_{1'}$	$J_{1,1'}$	$H_{(7a)}$	$J_{(7a),1}$	$J_{(7a),1'}$
(7; R = Ph, R' = H)	C_6H_6	4·09	3·76	−10·0	4·09	3·75	−3·7	2·67	2·28	−10·0	—	7·5	6·5
	$CDCl_3$	4·37	4·14	−9·8	4·38	4·01	−3·8	3·06	2·72	−10·4	—	7·8	6·6
5,5,7,7-tetradeuterio-(7; R = Ph, R' = H)	C_6H_6	4·11	3·78	−9·9	—	—	—	2·72	2·32	−10·2	3·34	7·9	6·9
(7; R = Ph, R' = Me)	$CDCl_3$	—	4·59	—	4·41	4·02	−4·1	3·28	2·80	−10·7	—	8·1	6·9
(7; R = Me, R' = H)	$CDCl_3$	4·31	4·13	−10·1	3·68	3·56	−3·8	3·02	2·67	−10·2	—	7·6	6·6

Table 7. Preparation of 3-, 3,3'- and 3,5-substituted perhydro-7a-methyloxazolo[3,4-*c*]oxazoles

Compound	b.p.	n_D^{23}/m.p.	Formula	Required C	Required H	Required N	Found C	Found H	Found N
3-ethyl	72–3/15 mmHg	1·4479	$C_8H_{15}NO_2$	61·1	9·6	8·9	60·8	9·5	9·2
3-i-propyl	56–8/3 mmHg	1·4482	$C_9H_{17}NO_2$	63·1	10·0	8·2	63·1	9·7	7·85
3-t-butyl	102–4/15 mmHg	1·4510	$C_{10}H_{19}NO_2$	64·8	10·3	7·6	65·0	10·4	7·6
3-phenyl	99–102/0·3 mmHg	1·5305	$C_{12}H_{15}NO_2$	70·2	7·4	6·8	70·4	7·6	6·8
3-*p*-methoxyphenyl	127–130/0·3 mmHg	1·5362	$C_{13}H_{17}NO_3$	66·4	7·3	5·95	66·1	7·5	5·8
3-*p*-chlorophenyl	115–120/0·2 mmHg	—	$C_{12}H_{14}NO_2Cl$	60·1	5·9	5·8	60·7	6·1	5·9
3-*p*-nitrophenyl		128–130°	$C_{12}H_{14}N_2O_4$	57·5	5·6	11·2	57·7	5·8	11·5
		88–90°	$C_{12}H_{14}N_2O_4$	57·5	5·6	11·2	57·6	5·4	11·3
3,3'-dimethyl	38–9/1 mmHg	1·4508	$C_8H_{15}NO_2$	61·1	9·6	8·9	61·05	9·6	9·2
3,3'-diethyl	92–3/10 mmHg	1·4582	$C_{10}H_{19}NO_2$	64·8	10·3	7·6	64·7	10·4	7·75
3,3'-spirocyclopentyl	87–8/3·3 mmHg	1·4813	$C_{10}H_{17}NO_2$	65·5	9·35	7·9	65·5	9·3	7·9
3,3'-spirocyclohexyl	82–4/1·5 mmHg	1·4841	$C_{11}H_{19}NO_2$	67·0	9·7	7·1	66·7	9·8	7·3
3,3'-spiro-4-t-butylcyclohexyl	120–2/1·2 mmHg	67°	$C_{15}H_{27}NO_2$	71·1	10·7	5·5	71·2	11·0	5·25
cis-3,5 diphenyl	—	111°	$C_{18}H_{19}NO_2$	76·8	6·8	5·0	77·1	7·0	5·0
trans-3,5 diphenyl	—	128°	$C_{18}H_{19}NO_2$	76·8	6·8	5·0	77·1	6·9	4·9
trans-3,5 di-*p*-chlorophenyl	—	121–3°	$C_{18}H_{17}NO_2Cl$	61·75	4·9	4·0	61·7	5·05	4·0
cis-3,5 di-*p*-chlorophenyl	—	57°	$C_{18}H_{17}NO_2Cl$	61·75	4·9	4·0	62·2	5·1	4·0
trans-3,5 di-*p*-nitrophenyl	—	195–7°	$C_{18}H_{17}N_3O_6$	58·2	4·6	11·3	58·5	4·6	11·6
cis-3,5 di-*p*-nitrophenyl	—	128–9°	$C_{18}H_{17}N_3O_6$	58·2	4·6	11·3	58·3	4·6	11·3

tion of the powders yielded separate samples of pale yellow needles, m.p. 88–90°.

General procedure for preparation of 3,5-*disubstituted-perhydro-*7a-*methyloxazolo*[3,4-c]*oxazoles.* The appropriate aldehyde (0·5 M) was added to a soln of 2-methyl-2-amino-1,3 propanediol (0·25 M) in absolute benzene (200 ml) and the mixture refluxed until the theoretical amount (0·5 M) of water had been collected in a Dean and Stark water separation apparatus. The benzene was removed *in vacuo* and the residual oil was either distilled under reduced pressure or allowed to crystallise prior to recrystallisation from EtOH or benzene. The experimental data are presented in Table 7.

*Perhydro-*3,5-*diphenyl-*7a-*methyloxazolo*[3,4-c]*oxazoles.* The crude product (90·5%) was carefully fractionally recrystallised from EtOH into two pure isomers and a number of mixed fractions. The isomer melting at 128° was less soluble, that melting at 111° more so. Both isomers crystallised as fine colourless needles.

*Perhydro-*3,5-*di-*p-*chlorophenyl-*7a-*methyloxazolo*[3,4-c]*oxazoles.* The crude product was taken up in warm xylene (50 ml) and cooled to 0°. The solid product which crystallised out was filtered off and recrystallised from EtOH as fine white needles m.p. 121–3°. The xylene mother liquors were treated with EtOH (100 ml), cooled to − 10° and the crystalline product filtered. Recrystallisation from EtOH afforded a white powder m.p. 57°.

*Perhydro-*3,5-*di-*p-*nitrophenyl-*7a-*methyloxazolo*[3,4-c]*oxazoles.* The crude product was dissolved in warm benzene (50 ml) and cooled to 0°. The solid product which crystallised was filtered off and recrystallised from the same solvent to give fine pale yellow needles, m.p. 128·5°. The other isomer was obtained by evaporation of the benzene to low bulk (*ca* 20 ml) when a waxy solid separated. Recrystallisation gave pale yellow waxy plates, m.p. 195–7°.

*Preparation of perhydro-*1-*phenyloxazolo*[3,4-c]*oxazoles.* A mixture if isomers of 2-amino-1-phenyl 1,3-propanediol[6] was treated with 37% aqueous formaldehyde soln with cooling to room temp. The mixture was then shaken for 30 min by which time two layers were observed. After basifying with conc NaOH, the mixture was extracted 3 times with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give a pale yellow viscous syrup which was distilled under vacuum. The fraction distilling at 104–8°/0·06 mmHg was collected as a mobile pale yellow oil and shown by analytical GLC to consist of two components of very close retention times. Separation was achieved using a $\frac{3}{4}$" column containing Grade III Woelm alumina (120 g) and eluting with a 10% solution of ether in 40–60° light petroleum. The spectra of the second isomer to be eluted from the column were found to be identical with those of the compound obtained when L-(+)-*threo*-2-amino-1-phenyl-1,3-propanediol was shaken with formaldehyde in slight excess of a two molar equivs and the resulting mixture basified and ether extracted as above. The oil recovered from the ether was distilled *in vacuo* to give a colourless mobile liquid at 110°/0·12 mmHg, n_D^{20} 1·5475. (Found: C, 69·0; H, 7·0; N, 7·2. $C_{11}H_{13}NO_2$ requires: C, 69·1; H, 6·85; N, 7·3%).

General procedure for preparation of 3-*substituted-*4-*ethyloxazolidines.* The appropriate aldehyde or ketone (0·2 M) was added to a soln of 2-amino-1-butanol in abs EtOH (250 ml). To the cooled soln was added Adams catalyst (0·2 g) and the mixture was hydrogenated at 50 psi on a Parr hydrogenator at room temp until the calculated volume of H_2 had been absorbed (12–36 hr). The catalyst was then filtered off, the EtOH removed under reduced pressure and the residue either distilled *in vacuo* or recrystallised from ether–light petroleum to give the N-substituted-2-amino-1-butanols. Experimental results are shown in Table 8. The N-substituted-2-amino-1-butanol (0·1 M) was treated with a slight excess of 37% formaldehyde soln and vigorously shaken until 2 layers were observed. The upper organic layer was extracted with ether and the combined ethereal extracts dried (Na_2SO_4), concentrated and distilled *in vacuo* to give the required oxazolidines. The experimental data are shown in Table 9.

Preparation of perhydro-imidazo[1,5-c]*thiazoles*

*Ethyl thiazolidine-*4-*carboxylate.* Thiazolidine-4-carboxylic acid (50 g) was suspended in specially dried abs EtOH (300 ml). The slurry was saturated with dry HCl during which the solid passed into soln. The soln was refluxed for 1 hr after which, on cooling, colourless plates of ethyl thiazolidine-4-carboxylate hydrochloride separated (71·3 g). This product was dissolved in a minimum of water and treated with saturated NaOH aq, which resulted in two layers. The organic layer was extracted with three 100 ml portions of ether, which were combined, dried (Na_2SO_4) concentrated and the resulting oil distilled. Ethyl thiazolidine-4-carboxylate was collected as a colourless oil b.p. 66·9°/0·03 mmHg (34·1 g) and was stored under N_2 at low temp.

Ethyl 2-*methyl-thiazolidine-*4-*carboxylate.* A mixture of L-cysteine ethyl ester hydrochloride (15 g), paraldehyde (5·1 g) in abs EtOH (80 ml) containing a small amount of dry HCl was refluxed for $\frac{1}{2}$ hr. The soln was then concentrated in vacuum to give a yellow oil which was triturated with ether yielding a white solid. The solid was separated, dissolved in a minimum of water and solid K_2CO_3 added until effervescence ceased when the mixture was ether extracted 3 times. The combined extracts were dried (Na_2SO_4) concentrated and the resulting oil distilled. Ethyl-2-methyl-thiazolidine-4-carboxylate was collected as a colourless oil 80–81°/0·95 mmHg (7·3 g), and was stored under nitrogen at low temp.

Table 8. Preparation of N-substituted-2-amino-1-butanols

N-Substituent	B.p.°/mmHg	n_D^{20}/m.p.	Formula	Required C	Required H	Required N	Found C	Found H	Found N
Me	105–6°/100	1·4436	$C_5H_{13}NO$	58·2	12·7	13·6	58·0	12·9	13·5
Et	95–7°/30	1·4467	$C_6H_{15}NO$	61·5	12·9	11·95	61·5	13·2	12·05
Pr'	—	43–44°	$C_7H_{17}NO$	64·1	13·1	10·7	63·95	13·3	10·4
Cyclohexyl	148–50°/30	50–50·5°	$C_{10}H_{21}NO$	70·1	12·4	8·2	69·95	12·6	8·0
Benzyl	170–1°/20	57–58°	$C_{11}H_{17}NO$	73·7	9·6	7·8	73·7	9·9	7·6
α-Methylbenzyl	108°/1	1·5178	$C_{12}H_{19}NO$	74·6	9·9	7·25	74·4	10·15	7·0

Table 9. Preparation of 3-substituted-4-ethyloxazolidines

Compound	B.p.°/mmHg	n_D^{20}	Formula	Required C	Required H	Required N	Found C	Found H	Found N
(6; R = Me)	69–70°/100	1·4403	$C_6H_{13}NO$	62·6	11·4	12·2	62·65	11·1	12·4
(6; R = Et)	83°/100	1·4457	$C_7H_{15}NO$	65·1	11·7	10·8	65·1	12·0	10·8
(6; R = Pr^i)	102°/100	1·4358	$C_8H_{17}NO$	67·1	12·0	9·8	66·8	12·1	9·8
(6; R = cyclohexyl)	112°/10	1·4739	$C_{11}H_{21}NO$	72·1	11·5	7·6	71·9	11·7	7·4
(6; R = benzyl)	130°/10	1·5139	$C_{12}H_{17}NO$	75·35	9·0	7·3	75·6	9·25	7·4
(6; R = α-methylbenzyl)	92°/1	1·5119	$C_{13}H_{19}NO$	76·05	9·3	6·8	75·8	9·6	6·7

General procedure for preparation of N-hydantoins. The ethyl thiazolidine-4-carboxylic acid (0·05 M) was dissolved in pyridine (15 ml) and treated dropwise with a slight excess of phenyl isocyanate. The resulting mixture was stood overnight when the solvent was removed *in vacuo* leaving a viscous yellow oil. Trituration with a small amount of EtOH produced a white solid which on addition of enough EtOH could be recrystallised. The N-phenyl hydantoin from ethyl thiazolidine-4-carboxylate was collected as fine white needles (6·8 g) m.p. 149–50°. (Found: C, 56·4; H, 4·4; N, 12·3; S, 13·7. $C_{11}H_{10}O_2N_2S$ requires: C, 56·4; H, 4·3; N, 12·0; S, 13·7%). The N-phenyl hydantoin from ethyl 2-methyl-thiazolidine -4-carboxylate was collected as fine white needles (6·2 g) m.p. 136–7°. (Found: C, 57·9; H, 5·0; N, 11·1; S, 12·9. $C_{12}H_{12}O_2N_2S$ requires: C, 58·1; H, 4·9; N, 11·3; S, 12·9%).

N-Methyl hydantoin of ethyl thiazolidine-4-carboxylate. Ethyl thiazolidine-4-carboxylate (8·0 g) was dissolved in pyridine (15 ml) and treated dropwise with methyl isocyanate (3·0 g) while swirling and cooling. The mixture was stood overnight after which the solvents were removed under high vacuum. The resulting yellow syrup did not solidify on trituration with EtOH. The IR and NMR spectra suggested that the ring had not closed and that the N-carbamoyl derivative had been formed. As a result, this syrup (5 g) was dissolved in EtOH (15 ml), a trace of solid KOH was added and the mixture refluxed for ½ hr. The solvents were then removed *in vacuo* and the remaining yellow oil taken up in ether and decanted from an orange gum. Removal of the solvent gave a colourless oil which crystallised rapidly. The solid was recrystallised from benzene–light petroleum to give white needles m.p. 50–51°.

General procedure for reduction of hydantoins to perhydro-imidazo[1,5-c]*thiazoles.* A soln of the hydantoin (4·7 g) in dry THF was dropped onto a stirred slurry of LAH (4·7 g) in dry THF at such a rate so as to keep the mixture refluxing gently. When all the solution had been added, the mixture was refluxed for 3 hr, after which excess hydride was carefully destroyed with water. The solid were filtered off and the filtrate was dried (Na_2SO_4) and concentrated to leave a solid residue, which was recrystallised.

Perhydro-6-phenyl-imidazo[1,5-c]*thiazole* was obtained from the N-phenyl hydantoin of ethyl thiazolidine-4-carboxylate as fine white needles (3·1 g) from ether–light petroleum, m.p. 118°. (Found: C, 64·3; H, 7·1; N, 13·4; S, 15·5. $C_{11}H_{14}N_2S$ requires: C, 64·1; H, 6·8; N, 13·6; S, 15·5%).

Perhydro-3-methyl-6-phenyl-imidazo[1,5-c]*thiazole* was obtained from the N-phenyl hydantoin of ethyl 2-methyl-thiazolidine-4-carboxylate as fine white needles (2·9 g) from EtOH, m.p. 230° (dec). (Found: C, 65·3; H, 7·4; N, 12·7. $C_{12}H_{16}N_2S$ requires: C, 65·4; H, 7·3; N, 12·7%).

Perhydro-6-methyl-imidazo[1,5-c]*thiazole* was obtained from the N-methyl hydantoin of ethyl thiazolidine-4-carboxylate as a colourless mobile liquid (3·1 g) 74–6°/3·5 mm. (Found: C, 50·0; H, 8·6; N, 19·4. $C_6H_{12}N_2S$ requires: C, 50·0; H, 8·4; N, 19·4%).

Perhydro-5,5,7,7-tetradeutero-6-phenyl-imidazo[1,5-c]*thiazole.* Preparation of this compound was achieved by using LAD in place of the hydride and carrying out the general procedure used on the N-phenyl hydantoin of ethyl thiazolidine-4-carboxylate. It was obtained as white needles from ether–petroleum ether, m.p. 117°.

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