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SYNTHESIS AND NMR STUDY OF NORBORNANE/NORBORNENE-FUSED TETRACYCLIC AZETIDINONES[1]

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ABSTRACT – Tetracyclic azetidinones 8, 9 and 12–17 were synthesized. In the cases of 8 and 9, the main component was isolated from the two-component product of the cycloaddition. The minor component was concentrated to give a mixture, from which a computer technique utilizing the known spectrum of the main component gave the proton resonance spectrum also of the minor component. Only one diastereomer could be isolated for the each of the analogues 12–17. Reaction of the 1,3-oxazine 3 with chloroacetyl chloride gave, besides the azetidinone 12, the 1,3-oxazine [2,3-b]-1,3-oxazin-4-one derivative 18. Configurations and conformations were determined by IR, ^{1}H and ^{13}C NMR spectroscopy.

INTRODUCTION

In view of the great medicinal importance of the penicillins and cephalosporins containing an azetidinone ring, increasing interest is attached to β-lactams.[2] The methylene-bridged, partly saturated 1,3-[3] and 3,1-benzoxazines,[4-6] prepared earlier in our laboratory, readily undergo cycloaddition reactions with chloroacetyl chloride to give fused-skeleton azetidinones. This extension of skeleton rigid norborne- or norbornane fused isomeric 1,3-oxazines is of stereochemical interest. These tetracyclic β-lactams also seem promising from the point of view of biological activity, since the norbornane moiety is a component of many active compounds.[7] In the recent literature[8,9] the development of new pharmaceuticals from norbornane derivatives has been reported.

Accordingly, the object of the present work is the conversion into tetracyclic azetidinones of the tricyclic, fused-skeleton 1,3-oxazine derivatives we had prepared earlier from the diexo and diendo 2-(hydroxymethyl)-bicyclo[2.2.1]hex-5-enyl-3-amines[4-6] and by 1,4-cycloaddition from norbornene, norbornadiene and (hydroxymethyl)benzamides,[3] together with elucidation of the structures of the isomeric azetidinones obtained in the "acid chloride reaction".[10]

SYNTHESIS

1,3-Aminoalcohols with norbornene skeleton, prepared by reduction from exo- and

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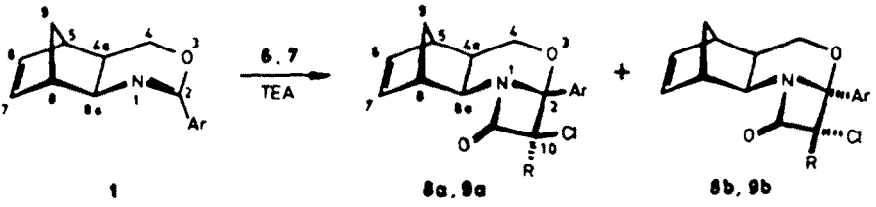
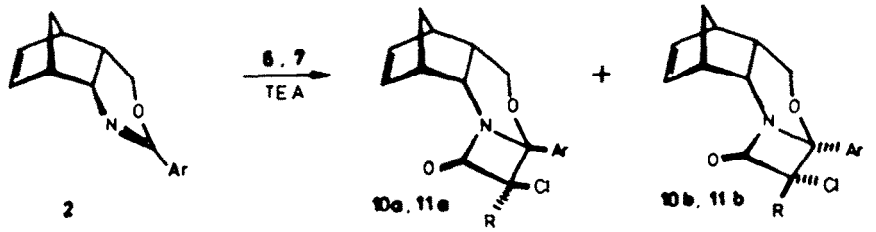
endo-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids,[4,11] were cyclized with imidates to 5,8-methano-2-(p-chlorophenyl)-r-4a,c-5,c-8,c-8a-tetrahydro-4H-3,1-benzoxazine (1) and 5,8-methano-2-(p-chlorophenyl)-r-4a,t-5,t-8,c-8a-tetrahydro--4H-3,1-benzoxazine (2).[4,6] The 2-substituted 5,8-methano-r-4a,c-5,6,7,c-8,c-8a-hexahydro-4H-1,3-benzoxazines (3 and 4) and 5,8-methano-2-(p-chlorophenyl)-r-4a, c-5,c-8,c-8a-tetrahydro-4H-1,3-benzoxazine (5) were synthesized from the appropriate (hydroxymethyl)benzamides by cycloaddition with norbornene and norbornadiene, respectively.[12]



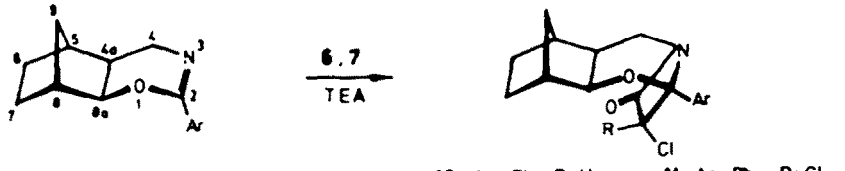
1 8a, 9a 8b, 9b

Ar *p*Cl-Ph; R H (8a,b) or Cl (9a,b)



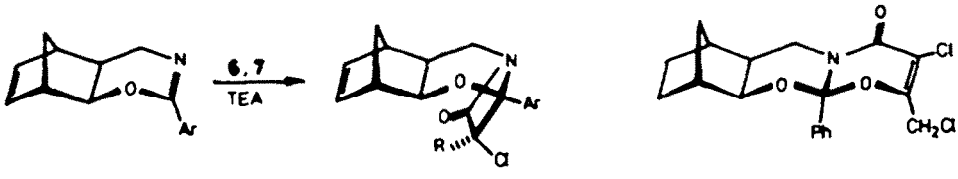
2 10a, 11a 10b, 11b

Ar *p*Cl-Ph; R H (10a,b) or Cl (11a,b)



3 Ar Ph
4 Ar *p*Cl-Ph

12 Ar Ph, R H 14 Ar Ph, R Cl
13 Ar *p*Cl-Ph, R H 15 Ar *p*Cl-Ph, R Cl



5

16 R H
17 R Cl

18

Ar *p*Cl-Ph

Compounds 1–5 were converted by means of chloroacetyl chloride (6) or dichloroacetyl chloride (7), in the presence of triethylamine, to the tetracyclic azetidinones 8–17. Two isomers each are possible for the tetracyclic dichloro derivatives (9, 11, 14, 15 and 17), which differ in the anellation of the oxazine and azetidinone rings, i.e. in the configuration of the carbon atom between the oxygen and nitrogen. In the case of the monochloro compounds (8, 10, 12, 13 and 16) two more isomers may exist, where the difference is in the mutual positions of the chlorine atom and the phenyl group. Two diastereomers each of 10 and 11 were isolated. Their

structure elucidation has previously been reported.[6] The new observation is now made that 11a (m.p. 137–139 °C) is converted, on heating to 180 °C, into the epimer 11b (m.p. 194–195 °C), i.e. the configuration of the 2R* carbon atom* changes to 2S*. Hence, 11b is the more stable isomer.

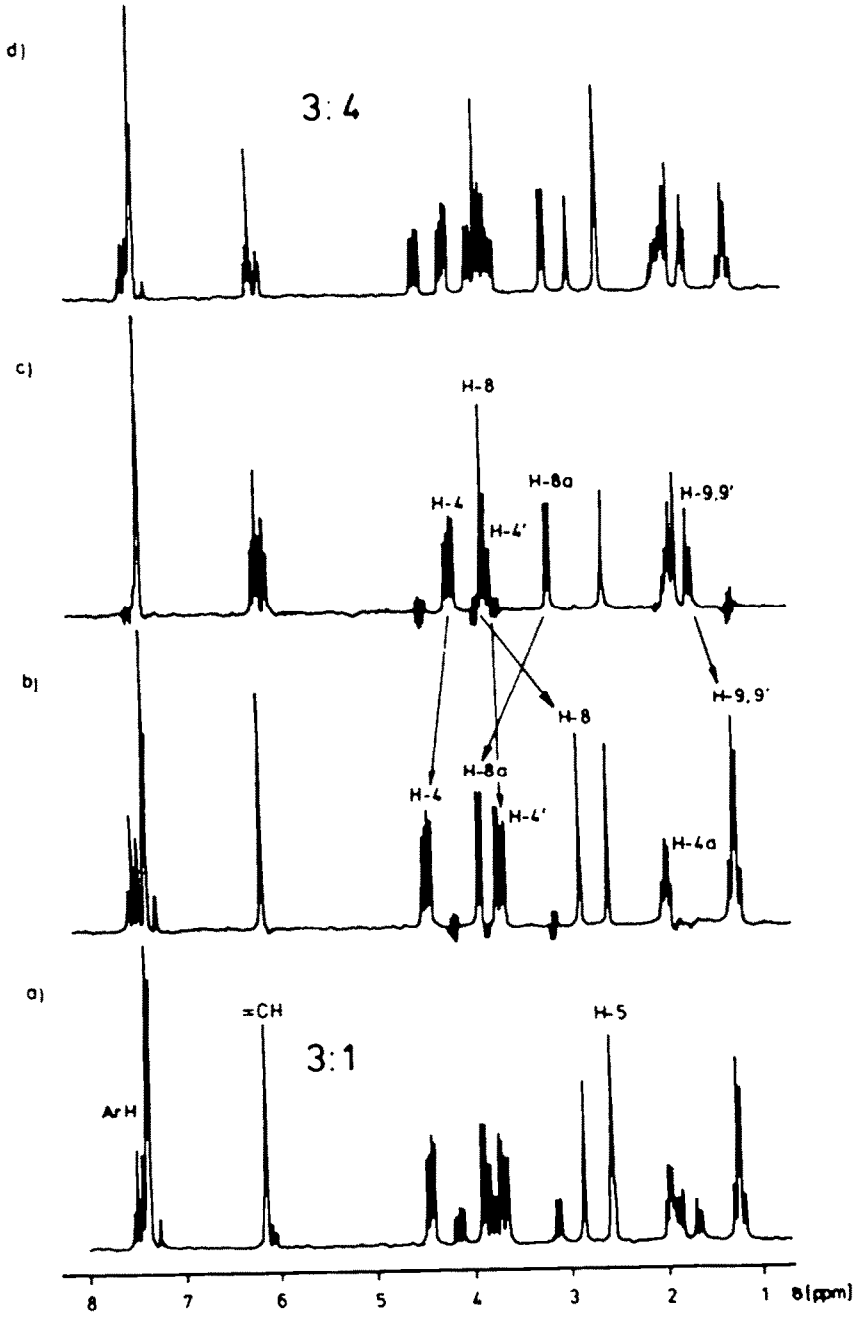


Fig.1. ^{1}H NMR spectra of two diastereomeric mixtures of compounds 9a and 9b, with 9a-9b-compositions (a) 3:1 (m.p.: 123–125 °C) and (d) 3:4 (m.p.: 81–83 °C), and the computer-constructed spectra of the homogeneous diastereomers (b) 9a and (c) 9b in $CDCl_3$ solution at 250 MHz.

* In the Experimental (in the chemical names of the compounds) the numbering according to the IUPAC nomenclature is followed. However, in the text including the Figures and the Tables the numbering is different and uniform for all compounds investigated, in order to facilitate comparison of the spectrally analogous data.

Table 1. ^{1}H NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds 8a,b, 9a,b and 12-18 at 250 MHz in $CDCl_3$ solution.[a,b]

Compound	H-4e' dd(1H)	H-4a' dd(1H)	H-4a m(1H)	H-5 s(1H)	H-6 dd(1H)[c]	H-7 dd(1H)[c]	H-8 s(1H)	H-8a d[d](1H)	H-9' endo[e]	H-9 exo[e]	H-10 s(1H)
8a	4.30	3.42	1.94	2.46	6.09	6.18	2.87	3.76	1.14	1.26[f]	4.95
8b	4.05	3.68	1.71	2.60	6.05	6.21	3.92	3.20	1.64[f]	1.81	4.98
9a	3.70	4.46	1.98	2.59	6.16 s (2H)		2.88	3.90	1.22	1.25	-
9b	4.17	3.80	1.85	2.59	6.08	6.18	3.84	3.14	1.68	1.87	-
12	3.93	2.56	∿ 2.35[g]	1.86	∿ 1.15[h], ∿ 1.5		2.40[g]	4.01	1.72	1.14[h]	5.26
13	3.92	2.53	∿ 2.35[g]	1.89	∿ 1.15[h], ∿ 1.5		2.41[g]	4.00	1.72	∿ 1.1[h]	5.25
14	3.99	2.56	∿ 2.45[g]	1.85	∿ 1.15[h], ∿ 1.5[i]		2.43[g]	4.37	∿ 1.55[i]	∿ 1.1[h]	-
15	3.99	2.52	∿ 2.40[g]	1.86	∿ 1.15[h], ∿ 1.5[i]		2.44[g]	4.36	∿ 1.55[i]	∿ 1.15[h]	-
16	4.03	2.53	∿ 2.30	2.47	5.94	6.23	2.99	3.96	1.51	1.74	5.19
17	4.10	2.53	2.36	2.48	5.95	6.23	3.04	4.31	1.52	1.61	-
18	4.52	3.05	1.82	2.05	0.90[j], 1.05[k], 1.50[l]		2.42	3.19	1.96	1.24	4.07[c] 4.24[e]

Notes: [a] IR νC=O band (cm^{-1}) in KBr: 1782 (8a, 13), 1774 (8b), 1792 (9a), 1770 (12), 1790 (14), 1803 (15), 1784 (16), 1801 (17) and 1672 (18); [b] Signal of the phenyl hydrogens: 7.40 (8a,b, 9b and 15), s, (4H), ∿ 7.38 and 7.46 (9a, 13 and 16) and 7.47 and 7.54 (17), resp., AA'BB'-type multiplet of 4H-intensity with very close central lines and 7.35-7.60, m, 5H (12, 14 and 18); [c] In case of 12-15 overlapping multiplets of 2-2H intensity (δH(exo) > δH(endo) ~19]); [d] dd due to J(8,8a) coupling (c.f. Table 2) in case of 8a,b and 9a; [e] A or B part of an AB multiplet (2H), J(A,B): see Table 2 (8a,b, 9a,b, 12-18), for H-4 atoms of 18: 12.2 Hz; [f] Both lines of the A (8a) or B (8b) part (δA > δB) of the AB multiplet split by 1.7 (8a) or 1.5 (8b) Hz to triplets; [g,h,i] Overlapping signals; [j] H-7(endo); [k] H-6(endo); [l] H-6',7'(exo).

The azetidinones prepared from compound 1 are also isomeric mixtures, from which only the main product could be isolated as a pure compound. The different solubilities and chromatographic properties of the isomers also permitted the isolation of some epimeric mixtures in which an isomer originally occuring merely as a by-product was present in higher concentration. Only one diastereomer each could be isolated from the mixtures of isomers 12-17.

The reaction of compound 3 with chloroacetyl chloride takes place in two directions: besides the azetidinone 12, a 1,3-oxazino[2,3b]-1,3-oxazin-4-one derivative (18) fused to norbornane and having a nitrogen bridgehead could also be isolated; i.e. a derivative formed by reaction with two equivalents of chloroacetyl chloride. The synthesis of monocyclic dihydrooxazines from acyclic imines with acetyl chloride has been reported.[13] The formation of diketene is assumed as the explanation of the reaction. Relatively simple bicyclic compounds of the aza-ortho-ester type have been prepared from dihydro-1,3-oxazine by means of epoxide addition.[14]

NMR SPECTROSCOPIC STUDY

COMPUTER CONSTRUCTED ^{1}H NMR SPECTRA AND STRUCTURE ELUCIDATION OF THE ANGULARLY FUSED DIASTEREOMERIC AZETIDINONES 8a,b AND 9a,b

The ^{1}H NMR chemical shifts of compounds 8a,b, 9a,b and 12-17 are listed in Table 1, and the more important proton-proton coupling constants can be found in Table 2. The principles of determining the configurations and conformations have been described in a previous paper,[6] and hence only the essential features will be given below.

For all compounds examined, the expected diexo anellation of the oxazine ring to the norbornane or norbornene skeleton is unambiguosuly proved by the small value of

Table 2. Vicinal coupling constants of compounds 8a,b, 9a,b and 12 – 18 in Hz.

Compound	J(4,4')	J(4,4a)	J(4',4a)	J(4a,8a)	J(5,6)	J(6,7)	J(7,8)	J(8,8a)	J(9,9')
8a	12.6	7.8	8.6	8.6	2.9	5.7	3.1	1.7	9.7
8b	12.3	6.4	8.0	7.3	3.2	5.7	3.1	0.6	9.7
9a	12.8	5.5	6.6	8.8				1.2	8.2
9b	12.1	6.6	12.2	7.2	3.2	5.7	3.0	< 1	10.1
12	13.4	8.5	11.8	6.1				< 1	10.4
13	13.3	8.3	11.7	6.1				< 1	9.0
14	13.5	8.9	12.0	6.2				< 1	11.4
15	13.0	8.4	11.4	6.1				< 1	?
16	13.5	8.2	11.7	6.2	3.2	5.7	3.0	< 1	∿ 9
17	13.6	8.6	11.5	6.4	3.1	5.8	2.9	< 1	9.3
18	13.2	8.1	11.5	6.7				< 1	10.5

the coupling constant J(8,8a) and the corresponding singlet and doublet structures of the H-8 and H-8a signal, respectively. Thus, the ring anellation remains unchanged during cyclization.

The structures of isomers 8a,b and 9a,b can be determined only in the knowledge of the spectral data on the homogeneous epimers. The computer of the Bruker WM-250 FT spectrometer was therefore utilized, and the spectra of the pure epimers, multiplied by an appropriate factor, were subtracted from the spectra of the isomeric mixtures, to obtain the spectra of the other epimers. The data derived in this way are given in Tables 1 and 2. The procedure is exemplified for two mixtures, with different compositions, of isomers 9a,b (Fig. 1).

A comparison of the spectral data reveals that in isomer 9a, isolated in the pure state and melting at 165 – 167 °C, the configuration of the C-2 atom is R*, i.e. the phenyl substituent is in the endo position; the other component of the mixture, 9b, is the 2S* exo-phenyl epimer. The main facts supporting this conclusion are as follows:

a) The H-9 and H-9' signals of compound 9a show a considerable upfield shift (0.62 and 0.46 ppm) as compared with epimer 9b. This is due to the anisotropic effect[15a] of the phenyl ring approaching H-9,9', causing shielding of the hydrogens situated "above" the plane of the ring.

b) The same effect can be observed for the H-8 signal; this signal is thus upfield shifted by 0.96 ppm as compared with that for 9b.

c) A downfield shift by 0.76 ppm, as compared with 9b, is found for the H-8a signal; this shift is due to the deshielding effect of the coplanar carbonyl group.[15b]

The directions of the above effects, unlike their magnitudes, are not influenced by the conformation of the flexible oxazine ring, and this must also be taken into account. As concerns the conformation, the deciding spectral data are the vicinal coupling constants of the C-4 methylene protons with H-4a. As shown by the molecular model, the oxazine ring may exist as two relatively stable conformers, which are interconvertible by ring inversion. Hence, when the configurations too are taken into account, there are four structures to be considered.

In the case of the configuration 9a with the twist-like conformation A (Fig. 2), O-3 is in the proximity of H-9'; the carbonyl oxygen is coplanar with H-8a, and H-4' (quasiaxial C-4 methylene hydrogen) is in the cis position to H-4a. The Newman projection viewed from the direction of the C-4,C-4a axis shows that the dihedral angles C-H(4a),C-H(4') and C-H(4a),C-H(4) are about 55° and 65°, respectively (Fig. 2). Couplings similar to each other in magnitude are therefore expected.

In the envelope-like conformation B, five atoms of the oxazine ring are nearly

coplanar; only O-3 lines out of the common plane. During inversion, the azetidinone ring moves "upwards" and the phenyl substituent "backwards": this does not cause considerable changes in the interactions described under (a)-(c), which are responsible for the mostly differing chemical shifts in the spectra of the isomers. There is, however, a decisive difference in the positions of the C-4 methylene hydrogens: the hydrogen in the cis position to H-4a (being parallel to the azetidinone ring) which in conformation A was axial is now in the equatorial position, while its equatorial trans counterpart in conformation A is now axial and situated above the plane of the phenyl ring. The dihedral angle made by C-H(4a),C-H(4a') is about 160°, whereas the C-H(4a),C-H(4e') angle is about 40°. Since the coupling constants J(4,4a) and J(4',4a) measured for 9a are 5.5 and 6.6 Hz, respectively, the preference of conformation A can be regarded as proved. Conformation A is favoured because of the smaller steric hindrance between the molecular skeleton and the phenyl ring in this case, and also because the phenyl group is here in the energetically more favourable quasiequatorial position relative to the oxazine ring, whereas in conformer B it should be quasiaxial.

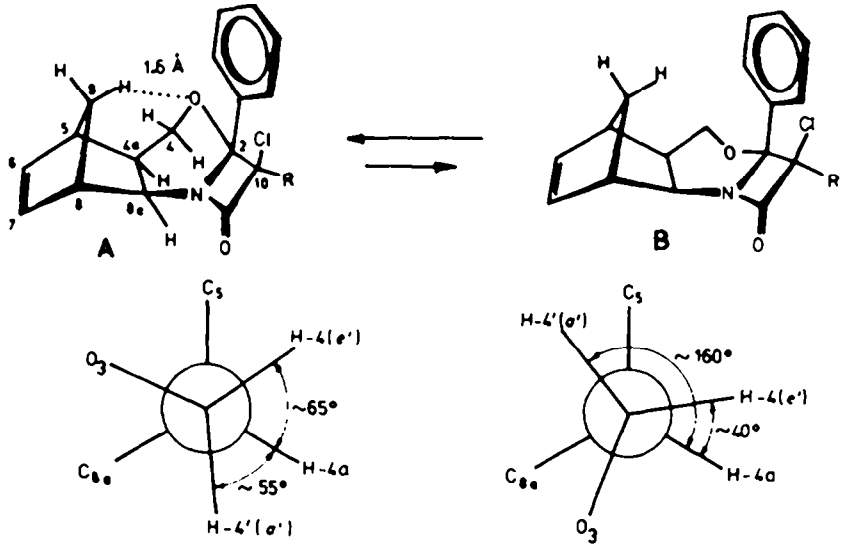


Fig. 2. Stable conformations of compounds 8a, 9a and the Newman projections from the direction of the C-4,C-4a axis.

The chlorine atom, which is trans to the phenyl ring in conformation A, is very close to H-4'(a'), with the notable consequence that the very general rule $\delta H_a < \delta H_e$, valid for cyclohexane and its hetero-analogues,[15c] is reversed in the case of 9a; the equatorial methylene hydrogen being the more shielded, while the chemical shift difference is also very marked (0.76 ppm).

This fact may be made the starting point in the determination of the C-10 configuration in the analogous monochloro-substituted analogue 8a. As compared with the epimer 8b, the 2R* configuration (endo phenyl group) can be inferred from the upfield shifts of H-8,9,9' signals and the downfield shift of H-8a signal, analogously to the case of 9a. On the other hand, conformation A, analogous to that of the dichloro compound 9a, follows from the similar coupling constants J(4,4a) and J(4',4a); 7.8 and 8.6 Hz. In the event of a similar stereostructure, a chlorine in trans position should give rise to a similar, anomalous shift relationship ($\delta H_a > \delta H_e$) for the C-4 methylene hydrogens. As this is not observed, the cis position of the phenyl and chlorine substituents relative to the azetidinone ring, and hence the R* configuration at C-10, are apparent. The assignments of the signals of the axial and equatorial methylene hydrogens are given on the basis of the relationship

J(4',4a) > J(4,4e), i.e. starting from the Karplus relation,[16] J(a,a)>J(a,e)>J(e,e). The steric position determined in this way for the chlorine atom is explained by the circumstance that, due to the coplanarity of the C_2—O_3 and C_{10}—Cl_{trans} bonds, a strong electrostatic repulsion would appear between a trans chlorine atom and the O-3; the molecule can avoid this by assuming the R* configuration at C-10. This phenomenon may be regarded as a special case of the anomeric effect[17,18] well known in carbohydrate chemistry.

By an analogous train of thought, the conformation of 9b is obtained as follows. In the case of near situated endo H-9' and O-3, it is the oxygen which lies out of plane of the hetero ring in the envelope-like conformation; the methylene hydrogen in the cis position with the quasiaxial H-4a is "above" the plane of the phenyl ring; the dihedral angles made by C-H(4a),C-H(4') and C-H(4a),C-H(4) are ∿ 40° and 80°, respectively, and H-8 is coplanar with the carbonyl group (conformation C, Fig. 3). Steric hindrance appears between H-9' and the chlorine atom in the trans position to the quasiaxial phenyl ring.

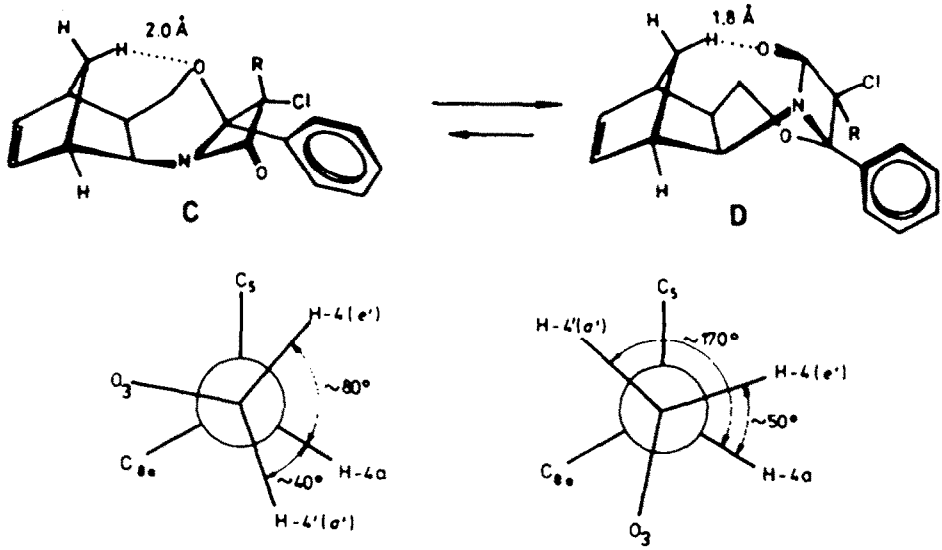


Fig. 3. Stable conformations of compounds 8b, 9b and the Newman projections from the direction of the C-4,C-4a axis.

In the inverse conformer D the six-membered hetero ring assumes the twisted boat form; the carbonyl oxygen remains in the proximity of H-8 and at the same time it also approaches close to the endo H-9'. In comparison to the situation in the stable conformer A of 9a, the methylene hydrogen, which is trans to H-4a and quasiaxial, is farther away from the chlorine, but nearer to the carbonyl oxygen. The dihedral angles C-H(4a),C-H(4) and C-H(4a),C-H(4') are now ∿ 50° and ∿ 170°, respectively. The phenyl ring is quasiequatorial and there is no steric hindrance between the trans chlorine and H-9'.

Thus, it is readily understandable that conformation D is the preferred one for compound 9b; unambiguous evidence in support of this is provided by the significantly different, but relatively high values of the coupling constants J(4,4a) = = 6.6 Hz and J(4',4a) = 12.2 Hz. The anomaly in the chemical shifts of the C-4 methylene hydrogens, observed in the case of 9a, is absent here; the signals of H-8 and H-9,9' are shifted downfield in comparison with those for 9a, due to the proximity of the carbonyl oxygen. On the other hand, the H-8a signal has suffered an upfield shift, since H-8a is farther removed from the carbonyl group and, as it is above the plane of the phenyl ring, it is more shielded.

Whereas the spectral data indicated the analogous conformation A for 8a and 9a, the spectral parameters of 8b suggest C as the preferred conformation. The most important evidence for this is given again by the similar and relatively smaller coupling constants J(4,4a) = 6.4 and J(4',4a) = 8 Hz, and also by the upfield shifts, which are slightly smaller for the signal of H-9, but higher for that of H-8 (0.55 and 1.05 ppm), than in the case of 8a (the corresponding differences in the pair 9a,b are 0.62 and 0.96 ppm). In the course of the inversion D → C the carbonyl oxygen is removed farther from H-9, and comes nearer to H-8. Conformation C is preferred in 8b, for in the absence of a trans chlorine atom the steric hindrance between the carbonyl oxygen and H-9' is suspended; though this hindrance does exist in the D form, the molecule can in this way eliminate the interaction between H-9' and Cl_{trans}, which would be even more unfavourable.

Conformation C is indicated by the upfield shift (3.68 ppm) of the H-4' signal as compared to 9b; in the C form H-4' is situated above the plane of the phenyl ring, and hence is more shielded. The preference of conformation C affords indirect evidence for the cis position of the chlorine atom and the phenyl ring (S* configuration of C-10); in the case of a trans chlorine (for the reasons described for 9b), conformation D would be preferred. Thus, the conformation of 8b is again explained by the anomeric effect.

ELUCIDATION OF THE STRUCTURES OF THE LINEARLY FUSED AZETIDINONES 12 – 17.

In the preparation of the linearly fused azetidinones, the main products 12-17 were isolated in stereohomogeneous form. Determination of their structures is fairly simple, since one of the two inverse conformations is unfavoured for both possible C-2 configurations, as a result of the considerable steric hindrance. Accordingly, for conformationally homogeneous "quasi-rigid" systems it is sufficient to elucidate the configurations at C-2, and for the monochloro derivatives those at C-10. This is substantiated by the fact that for all linearly fused compounds it holds that J(4,4a)<J(4',4a), the values of the J(4,4a) lying in the range 8.2-8.9 Hz, and those of J(4',4a) in the range 11.4-12.0 Hz (Table 2). In the favoured boat conformation, the dihedral angles of C-H(4a),C-H(4) and C-H(4a),C-H(4') bonds are ∿ 160° and ∿ 40°, respectively, whereas in the sterically unfavoured counterparts the same C-H bonds woud give dihedral angles of about 40° and 80°.

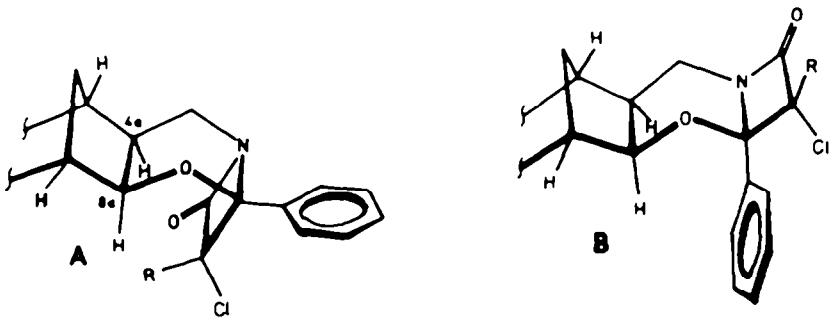


Fig. 4. Two diastereomeric structures of compounds 12-17, differing in configuration (2S* or 2R*) about the C-2 atom.

In view of the stable conformation, the S* configuration (A) at C-2 requires the quasiequatorial position of the phenyl substituent, and quasiaxial azetidinone ring (Fig. 4). The carbonyl oxygen is in the vicinity of H-4a, while the chlorine or hydrogen atom (which is trans to the phenyl ring, relative to the azetidinone ring) is in the proximity of H-8a.

The reverse situation is valid in the 2R* isomer (B) (Fig. 4). The β-lactam ring is quasiequatorial, the phenyl ring is quasiaxial, and H-4a,8a are situated

above the plane of the phenyl ring.

For structure A (2S*), therefore, a downfield shift of the H-4a signal would be expected, while the opposite shift of the H-4a and H-8a signals in conformation B (2R*).

In view of the data listed in Table 1, structure A, i.e. the S* configuration of C-2, can be assumed on the basis of the following arguments:

a) The H-4a atom is less shielded than in compounds 8a,b and 9a,b (the H-4a signal is shifted from 1.71-1.98 ppm into the region 2.30-2.45 ppm).

b) The H-8a shifts cannot be compared directly, as the neighbouring nitrogen is replaced by oxygen. However, it is known[15d] that the presence and vicinity of an amide nitrogen, e.g. in cyclohexanes, causes a geminal proton deshielding about 0.7 ppm greater than in the case of an ether oxygen substituent; accordingly, the observed downfield shift of the H-8a signal can be rationalized only by structure A.

c) A deciding argument in favour of configuration A is the very marked shift difference in the H-8a signals of the mono- and dichloro derivatives (0.36, 0.36 and 0.35 ppm for the pairs 12 - 14, 13 - 15 and 16 - 17, respectively.) The downfield shifts observed for the dichloro compounds are explained by the anisotropic effect of the chlorine atom.[15e] In the B isomers both chlorine atoms are far from H-8a, whereas in epimer A the chlorine trans to the phenyl ring is very close to H-8a. This is evidence of the cis position of the chlorine and phenyl substituents of the azetidinone ring, and of the S* configuration at C-10 in the monochloro compounds 12, 13 and 16.

The analogous structures of compounds 12-17 are obvious from the spectral data. Some proton resonance data on these compounds support the correctness of our conclusions concerning the stereostructures of the structural isomers 8a,b and 9a,b. Thus, the similar H-9,9' shifts for 8b and 9b, and for 16 and 17, confirm the exo (2R*) configuration of the phenyl ring in the former compounds, and hence the endo-phenyl (2S*) configuration in 8a and 9a. The similar values of the coupling constants J(4',4a) for 12-17 and for 9b are evidence of conformation D for the latter compound. This differs from that of its counterpart 9a, and indirectly substantiates conformation A for 9a and 8a, and conformation C for 8b.

Finally, attention should be drawn to some other chemical shifts for compounds 12-15, which have a norbornane skeleton; these shifts are explained by the absence of the inductive and anisotropic effects of the C_6–C_7 double bond operating in the norbornene derivatives 8a,b, 9a,b, 16 and 17. The olefin hydrogen signals in the range 5.94–6.24 ppm are here substituted by the saturated methylene signals at about 1.5 and 1.15 ppm. The two signals correspond to the endo and exo hydrogens.[19] The exo H-9 in compounds 12-15 is considerably more shielded, due to the lack of the deshielding effect of the double bond.[20] On the other hand, the upfield shifts of the H-5,8 signals must be due to the absence of the -I effect of the olefinic bond.[15f]

CARBON RESONANCE DATA ON THE AZETIDINONES

The carbon resonance shifts (Table 3) are in accordance with the structures of the compounds.

The data on pairs 8a,b and 9a,b could not be compared, as only isomers 8a and 9a were isolated as pure substances. However, the majority of the signals of isomer 8b could be identified from examination of a mixture containing this isomer as the main component. When these data are compared with those for 8a, the increased shielding of C-9 in 8a is marked. This is a consequence of the steric hindrance from the endo phenyl group (steric compression shift[21]). The same effect is responsible for the increased shielding of C-10 in compounds 12, 13 and 16 as compared with the posi-

Table 3. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds 8a,b,9a and 12–18 in $CDCl_3$ at 20 MHz.[a]

Compound	C-2	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9	C-10	C = O
8a	91.0	67.5	44.6[b]	44.8[b]	136.5[c]	137.6[c]	47.7	51.6	32.1	66.4	166.8
8b[f]		66.3	44.1[b]	44.4[b]	134.6	139.5	45.0	53.4	37.3	65.8	
9a	93.4	66.8	44.7[b]	45.0[b]	136.0	139.1	46.5	51.6	34.1		164.8
12	89.9	45.9	42.8[b]	39.2[b]	29.2	23.8	39.8[b]	76.6	33.6	63.5	165.8
13[e]	90.6	46.7	43.6[b]	40.2[b]	30.1	24.7	40.9[b]	77.3	34.7	64.2	166.9
14	92.9	43.8	43.2[b]	38.9[b]	29.1	23.6	39.5[b]	78.5	33.7	91.2	163.4
15	92.6	43.8	43.2[b]	38.9[b]	29.1	23.6	39.6[b]	78.6	33.7	90.2	163.4
16	89.6	43.8[d]		41.5	134.4	140.8	48.4	72.6	40.5	63.2	165.8
17[g]	93.6	45.0	45.1	39.7	133.5	142.3	49.9	76.2	42.0	91.3	163.8
18[h]	110.4	42.0	40.7	38.8	27.8	25.2	40.7	79.0	33.5	-	157.8

Notes: [a] The lines of the benzene ring appear in the ranges as follows: C-1': 133.9–136.8, C-2'–6': 126.4–130.1 (In case of 9a the C-2',6' and C-3',5' signals are split due to restricted rotation of the benzene ring), C-4': 135.0–136.6 (8a, 9a, 13, 15–17), 128.9 (12), 129.2 (14) and 130.5 (18); [b,c] Reversed assignment is also possible; [d] Two overlapping signals; [e] In DMSO-d_6; [f] In the spectrum of a mixture of 8a and 8b it was not possible to identify all lines of 8b; [g] Order of carbons determined by DEPT measurements; [h] CH_2Cl: 41.3; =CCl: 107.3; =C–O– : 153.2 ppm.

tional isomers 8. This supports the (2S*) configuration A, in which the trans H-10 atom is in steric hindrance with H-8a. The presumably even greater analogous effect of Cl-10 for the dichloro compounds could not be observed, as the data on 9a,b were not available.

STRUCTURE OF COMPOUND 18

The IR spectrum of compound 18 does not display the characteristic azetidinone carbonyl band.[22] Instead, the amide-I band at 1672 cm^{-1}, typical of simple amides, can be observed, precluding the possibility of a β-lactame structure. The amide-III band, characteristic of N-substituted δ-lactams,[23] is found at 1415 cm^{-1}. Besides the characteristic bands of the aromatic and aliphatic groups, the spectrum exhibits intense bands between 1300, and 945 cm^{-1} due to polar bonds as C-O, C-Cl or C-N.

The ^1H NMR data (Table 1) afford evidence for the presence of the norbornane skeleton and the phenyl ring. The downfield shift of the H-4,4' signals can be accounted for the anisotropy of the carbonyl group. The doublet split of the H-8a signal proves the unchanged diexo anellation of the norbornane and oxazine rings; the considerable upfield shift (≈ 0.8 ppm) of this doublet relative to that for the azetidinones 12–17, together with the somewhat smaller (≈ 0.6 ppm) H-4a shift in the same direction, reflects the parallel, "endo" position of the phenyl ring (R* configuration at C-2), since the anisotropic effect of the phenyl ring increases the shielding of H-4a,8a. In accord with this, H-9'(endo) is less shielded than in compounds 12–17. The conformation of the oxazine ring is the same as in the case of azetidinones 12–17; this follows unequivocally from the coupling constants $J(4,4a) = 8 < J(4',4a) = 11.5$ Hz. In this conformation, if the configuration were C-2R* (exo phenyl), increased shielding of H-9' would be observed, as a consequence of the proximity of the phenyl ring. The downfield shift of the H-5 signal by about 0.2 ppm is explained by the vicinity of the carbonyl group. Finally, the increased shielding of H-7(endo) is also attributable to the anisotropy of the phenyl group.

Further evidence for the proposed structure of 18 has been obtained by ^{13}C NMR. When the nine carbon signals of the norbornane-fused oxazine skeleton are compared with the signals of azetidinones, only the chemical shift of C-2 (110.4 ppm) is

appreciably altered: a downfield shift of about 20 ppm is observed. This is clear proof of the presence of a carbon in the vicinity of the three hetero atoms. (The analogous shifts for trimethyl and triethyl orthoformates are 115.0 and 112.5 ppm, resp.[24,25]) The signal of the chloro-substituted carbon is shifted to the range characteristic of olefins (107.3 ppm); the signals of the two carbons originating from the reaction of the second chloroacetyl chloride molecule are found at 41.3 (chloromethyl carbon) and 153.2 ppm (carbonyl group). The very large shift of the olefin signal is explained by the oxygen substitution and the electron distribution in the conjugated ene-one system; the preference for the limiting sturcture shown on the right-hand side of the mesomeric system $\text{C=C-C=O} \leftrightarrow \text{C}^{+}\text{-C=C-O}^{-}$ means that the electron density around the 3-carbon is drastically reduced.[15g]

EXPERIMENTAL

IR spectra were run in KBr discs on a Bruker IFS-113v FT spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ solution in 5 and 10 mm tubes, on Bruker WM-250 (^{1}H) and WP-80 SY (^{13}C) FT spectrometers at 250.13 (^{1}H) and 20.14 (^{13}C) MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: sweep width 5 kHz, pulse width 1 (^{1}H) and 3.5 (^{13}C) μs (~ 20° and ~ 30° flip angle), acquisition time 1.64 s, number of scans: 16 (^{1}H) and 1K-4K (^{13}C), computer memory 16K. Complete proton noise decoupling (~ 3 W) for the ^{13}C spectra, and Lorentzian exponential multiplication for signal-to-noise enhancement were used, line width 0.7 (^{1}H) and 1.0 Hz (^{13}C).

Preparation of compounds 8-17 (colourless crystalls, Table 4) rel-(1R,2R,5R,6R,9S,10S)- (8a) and rel-(1R,2R,5S,6S,9S,10S)-6-chloro-5-p-chlorophenyl-7-oxo-8-aza-4-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{5,8}$]tridec-11-ene (8b), rel-(1R,2R,5R,9S,10S)- (9a) and rel-(1R,2R,5S,9S,10S)-6,6-dichloro-5-p-chlorophenyl-7-oxo-8-aza-4-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{5,8}$]tridec-11-ene (9b), rel-(1R,2S,5R,6R,9R,10S)- (10a) and rel-(1R,2S,5S,6S,9R,10S)-6-chloro-5-p-chlorophenyl-7-oxo-8-aza-4-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{5,8}$]tridec-11-ene (10b), rel-(1R,2S,5R,9R,10S)- (11a) and rel-(1R,2S,5S,9R,10S)-6,6-dichloro-5-p-chlorophenyl-7-oxo-8-aza-4-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{5,8}$]tridec-11-ene (11b), rel-(1R,2S,4S,5R,9R,10S)-5-chloro-4-phenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridecane (12), rel-(1R,2S,4S,5R,9R,10S)-5-chloro-4-p-chlorophenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridecane (13), rel-(1R,2S,4S,9R,10S)-5,5-dichloro-4-phenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridecane (14), rel-(1R,2S,4S,9R,10S)-5,5-dichloro-4-p-chlorophenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridecane (15), rel-(1S,2S,4S,5R,9R,10R)-5-chloro-4-p-chlorophenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridec-11-ene (16), and rel-(1S,2S,4S,9R,10R)-5,5-dichloro-4-p-chlorophenyl-6-oxo-7-aza-3-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{4,7}$]tridec-11-ene (17). General procedure. The 1,3-oxazine 1, 2, 4, 5 (2.60 g; 0.01 mol) or 3 (2.25 g) was dissolved in dry benzene (5 ml) and a solution of 6 (1.10 g; 0.01 mol) or 7 (1.5 g; 0.01 mol) in benzene (5 ml) was added dropwise, with stiring, followed by the addition of TEA (1.0 g; 0.01 mol) dissolved in benzene (5 ml). The mixture was heated at 50 °C for 10 min and, after cooling, the solid was removed by filtration. The residue obtained on evaporation of the filtrate was applied to a silica gel column and eluted with benzene. The evaporation residue of the eluate was crystallized from a 1:1 mixture of benzene and petroleum ether to yield compound 8a, 9a, 10a, 11a or 12→17. Fractional crystallization of the material contained in the mother liquor gave the isomer 10b or 11b, or (in the cases of 8 and 9) an isomeric mixture, which was investigated as described above. The purity of the product was checked by DC (Kieselgel, benzene-ethanol-petroleum ether, 6:1:3).

rel-(1S,2S,4R,11R,12R)-7-Chloro-6-chloromethyl-8-oxo-4-phenyl-9-aza-3,5-dioxatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadec-6-ene (18). Compound 3 (2.25 g; 0.01 mol) was allowed to react with 6 (4.5 g; 0.04 mol) and TEA (4.0 g; 0.04 mol), as described above. Compound 12 crystallized first; fractional crystallization of the material in the mother liquor, using a mixture of benzene and petroleum ether, gave compound 18 (Table 4).

Epimerization of 11a. 11a (0.30 g, m.p. 137-139 °C) in a dry flask was heated in an oil bath at 180 °C for 5 min. After cooling, the residue was dissolved in benzene, applied to a silica gel column, and eluted with benzene. The crude product obtained on evaporation of the eluate and crystal-

Table 4. Physical and analytical data on compounds 8a,b – 11a,b and 12 – 18.

Compound	M.p. °C	Yield %	Formula	Molecular weight	Analitical data (%), calculated			found		
					C	H	N	C	H	N
8a	154-156	37	$C_{17}H_{15}NCl_2O_2$	336.22	60.73	4.50	4.17	60.50	4.27	4.12
8b[a]	56-58							60.84	4.61	4.05
9a	165-167	30	$C_{17}H_{14}NCl_3O_2$	370.67	55.09	3.81	3.78	55.05	3.79	3.57
9b[b]	81-83							55.02	3.80	3.59
10a	180-182	18	$C_{17}H_{15}NCl_2O_2$	336.22	60.73	4.50	4.17	60.54	4.32	4.11
10b	146-148	21						60.81	4.56	4.11
11a	137-139	17	$C_{17}H_{14}NCl_3O_2$	370.67	55.09	3.81	3.78	54.93	3.75	3.70
11b	194-195	24						54.85	3.72	3.65
12	140-141	34	$C_{17}H_{18}NClO_2$	303.79	67.21	5.97	4.61	67.30	5.99	4.68
13	171-173	39	$C_{17}H_{17}NCl_2O_2$	338.24	60.36	5.07	4.14	60.29	5.02	4.17
14	127-129	40	$C_{17}H_{17}NCl_2O_2$	338.24	60.36	5.07	4.14	60.53	5.14	4.03
15	140-142	44	$C_{17}H_{16}NCl_3O_2$	372.68	54.79	4.33	3.76	54.48	4.13	3.82
16	162-164	42	$C_{17}H_{15}NCl_2O_2$	336.22	60.73	4.50	4.17	60.79	4.58	4.03
17	108-109	37	$C_{17}H_{14}NCl_3O_2$	370.67	55.09	3.81	3.78	55.21	3.90	4.01
18	188-190	26	$C_{19}H_{19}NCl_2O_3$	380.27	60.01	5.04	3.68	60.14	5.19	3.58

Notes: [a] Diastereomeric 1:3 mixture of 8a and 8b; [b] Diastereomeric 3:4 mixture of 9a and 9b.

lized from a 1:1 mixture of benzene and petroleum ether was the epimer 11b (colourless crystals, m.p. 194-195 °C), having identical IR, ^1H and ^{13}C NMR spectra with 11b.

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