CYCLISATION AND SOLVOLYSIS OF STEREOISOMERIC 4-TERT-BUTYL-2-AMINOMETHYLCYCLOHEXANOL DERIVATIVES*

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Synthesis of four stereoisomeric 4-tert-butyl-2-aminomethylcyclohexanols and their N-benzoyl O-methanesulphonyl derivatives is described. The reaction of the "*trans*"-isomers in anhydrous ethanol gives exclusively the corresponding dihydrooxazines whereas the "*cis*"-isomers afford only products of solvolysis. Possible geometry of the transition state of the cyclisation reaction is discussed on the basis of the reaction rates.

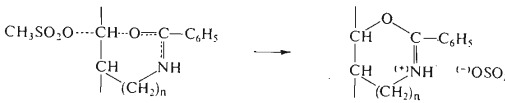
Within the framework of our stereochemical investigations we have studied extensively cyclisation reactions of cyclic[1,2] as well as open-chain[3] 1,2-amino alcohol derivatives. In one of our papers on this subject[2] we reported a study of the behaviour of the two "*cis*"- and the two "*trans*"-2-aminocyclohexanol derivatives *I*–*IV* under "solvolytic" conditions (heating in ethanol in the presence of potassium acetate). Both the "*trans*"-isomers were found to give rise to product indicative of a concerted intramolecular substitution process (Δ^2-oxazolines) with inversion of configuration (Scheme 1, *a*), whereas the "*cis*"-isomers gave only solvolysis products (olefin, acetate, *etc.*). A consideration of the two "*trans*"-isomers *III* and *IV* showed beyond any doubt that the "*trans*"-isomer *IV* cannot be reacting by way of a "triaxial" reaction path (Scheme 2, *A*) and it was suggested at the time that it probably reacts by way of a boat-type transition state (Scheme 2, *B*). A second alternative which, however, we did not mention in our original paper may be formulated,** namely that the benzamido group reacts in the chair-like form (Scheme 2, *C*) so to speak "round" the ring***,†.

* Part LXXX in the series Stereochemical Studies; Part LXXIX: This Journal *39*, 555 (1974).

** This alternative has been in particular stressed in discussion by the late Professor S. Winstein, University of California.

*** The same alternative may be suggested for the reaction of diequatorial isomer of 2-benzamido-3-methanesulphonyloxy-*trans*-decalin, described by Wylde and collaborators[4].

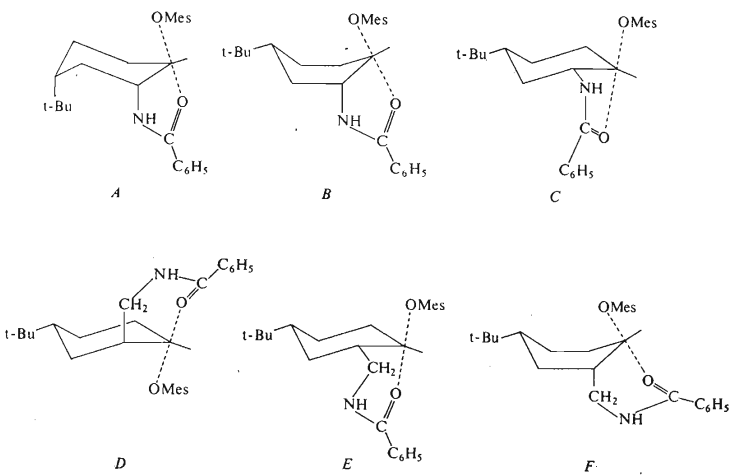
† Although there is — as evidenced by models — a distinct difference between the "boat" and "chair" transition state (Scheme 2,*B*,*C*) these forms in principle may near each other by flattening of the ring, and they eventually merge into a single "planar" conformation reminding a cyclohexanone chair–boat transition form. If the reaction proceeded by way of this conformation the whole problem would of course be meaningless; however, since the chair–boat transition form is known[5] to be high in energy, we assume that this form is not involved in the reaction path.



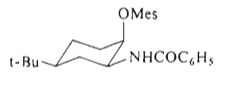
a: n = 0 *b*: n = 1

SCHEME 1

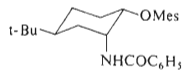
Since this question – as such, as well as its implications – appeared to be of considerable interest, we have now decided to study a cyclisation reaction of 1,3-derivatives, *i.e.* 2-benzamidomethyl-4-tert-butylcyclohexyl methanesulphonates *Vd–VIIId* which are again conformationally biased and their ground state geometry is analogous. Such study is of interest for several reasons. The ring of the transition state in the intramolecular displacement (Scheme 1, *b*) is here six-membered: there might be therefore greater possibility for the amide moiety to "reach around the ring" to the rear side of the carbon carrying the methanesulphonyloxy group; consequently, there might be an opportunity to observe an intramolecular ring closure from "*cis*"-derivatives to a *trans*-dihydrooxazine.



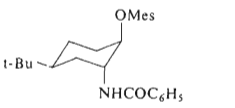
SCHEME 2



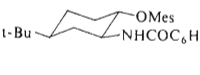
I



II



III

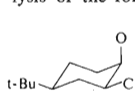


IV

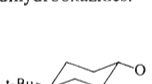
Moreover, the comparison of the reaction rates of *Vd*–*VIIId* with that described for the 4-tert-butyl-2-methylcyclohexyl toluenesulphonates[6] (*XIa*–*XIVa*) could also provide information about the effect of the neighbouring group participation on the reaction rates.

Synthesis

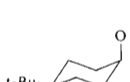
In view of the fact that suitable starting materials, such as the epoxide *XVIII*, the 5-tert-butyl-2-hydroxycyclohexanecarboxylic acids *XV* and *XX* and 4-tert-butyl--2-hydroxymethylcyclohexanol were available to us from earlier work[7,8], the synthesis of the four stereoisomeric 4-tert-butyl-2-aminomethylcyclohexanols proved to be a relatively simple matter. The method actually adopted depended on the availability of the particular starting compounds. The routes are outlined in Scheme 3 and require little comment. As will be pointed out, the "*trans*" isomers can be converted in almost quantitative yields into the corresponding "*cis*"-isomers by heating the N-benzoyl-O-methanesulphonyl derivatives in ethanol followed by acid hydrolysis of the formed dihydrooxazines.



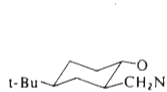
V



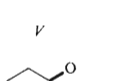
VI



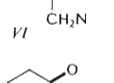
VII



VIII



IX



X

a: O = OH, N = NH_2
b: O = OH, N = $NHCOC_6H_5$
c: O = OH, N = $NHCOC_6H_4NO_2(p)$
d: O = OMes, N = $NHCOC_6H_5$
e: O = OMes, N = $NHCOC_6H_4NO_2(p)$
f: O, N = $-O-C(C_6H_5)=N-$

All the four possible dihydrooxazines *Vf – VIIIf* were prepared from the corresponding amino alcohols by treatment with ethyl benzimidate[9]; the relatively facile formation of *VIIf* from *VIIa* is interesting, because the cyclohexane ring in the arising dihydrooxazine must be highly strained.

RESULTS AND DISCUSSION

The rate constants for the reactions of compounds *Vd,e – VIIId,e* at 70°C and the thermodynamic parameters are summarised in Table I, together with the values of the derivatives *IXd,e* and *Xd,e*.

Reaction of cis-*Isomers*

Both the *cis*-isomers *Vd* and *VId* react to give products which would have been expected from a solvolytic reaction. Interestingly, the reaction mixture of the isomer *Vd* afforded in very low yield (6%) an oily base (picrate m.p. 189 – 190°C) which was not identical with any of the four possible stereoisomeric dihydrooxazines (IR-spectra

TABLE I

Rate Constants and Thermodynamic Parameters for the Reaction of *Vd,e – Xd,e* in Ethanol, Computed for 70°C

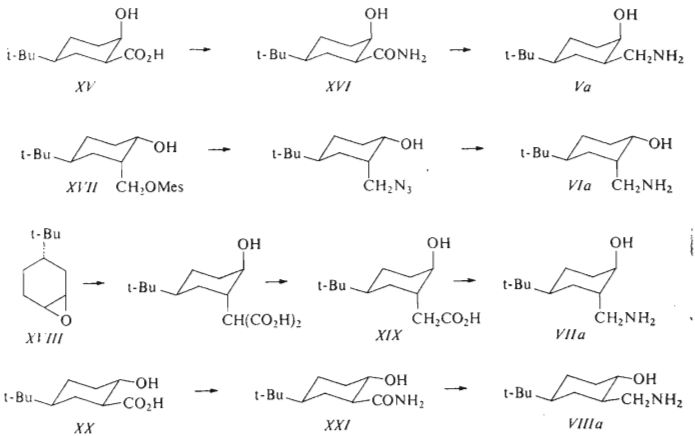
The rate constants were evaluated graphically; the values $\Delta H^{\neq}$ were obtained from the gradient of the plots of log k/T against the reciprocal of the absolute temperature. The values of $\Delta S^{\neq}$ were calculated from the Eyring equation[10].

Compound	$k \cdot 10^5$	$\Delta H^{\neq}$	$\Delta S^{\neq}$	k_H/k_{NO_2}
Vd	6·95	26·7	− 1·5	1·2
Ve	5·76	25·3	− 4·5	
VId	21·8	25·6	− 1·0	1·5
VIe	14·6	26·2	0·0	
VIId	131	22·7	− 6·0	2·9
VIIe	45·4	21·9	−10·5	
VIIId	23·3	24·5	− 4·0	2·2
VIIIe	10·6	24·5	− 5·5	
IXd	4·75	27·9	+ 3·0	1·0
IXe	4·65	27·1	+ 0·5	
Xd	24·5	22·2	−10·5	2·1
Xe	11·7	24·9	− 4·0	

and m.p.'s of the picrates). The molecular weight of this base was 271 and we suppose, on the basis of its NMR spectrum, that it has the oxazoline structure *XXII*. Such a compound would arise as a product of rearrangement during the solvolysis, analogously as in the acetolysis of *XIa* where the only substitution products are rearranged tertiary acetates[6]. The epimer *VId* did not afford any base. No dihydrooxazine could be detected, although orientation experiments showed that all the four dihydrooxazines are stable under reaction conditions and that already 10% of the dihydrooxazine was safely detectable (as picrate) in a simulated reaction mixture.

As was already pointed out[1,3], the ratio of reaction rate of an N-benzoyl (k_H) and N-*p*-nitrobenzoyl (k_{NO_2}) derivative may serve to estimate the extent of participation. As seen from Table I, the respective k_H/k_{NO_2} values for the *cis*-isomers of the type *V* and *VI* are only 1·2 and 1·5 (similarly as in the case[11] of the 1,2-derivatives *I* and *II*) showing thus that the participation of the benzamido group in these isomers, if any, is insignificant.

If this is so, then the reaction rates of the *cis*-isomers *Vd* and *VId* should be similar to the rates of the corresponding "*cis*"-4-tert-butyl-2-methylcyclohexyl tosylates *XIa* and *XIIa*[6]. The reaction rates are indeed similar (*Vd* reacts only about 8 times



SCHEME 3

and *VId* about 2·5 times more slowly than calculated* for *XIb* and *XIIb*, (see Table II), showing at the same time that the retarding polar effect of the benzamido group, which is considerable in the 1,2-series[2], is in the 1,3-series almost negligible.

Thus, we may conclude that, under conditions of measurements, the *cis*-isomers react by a normal unassisted solvolytic reaction and that the formation of the corresponding *trans*-dihydrooxazines, if any, is negligible.

Reaction of trans-*Isomers*

As shown by preparative experiments, the "*trans*"-isomers *VIId* and *VIIId* afforded dihydrooxazine derivatives *VIf* and *Vf*, respectively, as sole products in practically quantitative yields. The *cis*-configuration of the arising dihydrooxazines was proved by their identity with samples prepared from the corresponding *cis*-amino alcohols *VIa* and *Va*. The rate of the "diaxial" derivative *VIId* is only about 5 times greater than that of the "diequatorial" isomer *VIIId*; this is in contrast with the 1,2-amino alcohol series[2] where the ratio k_{III}/k_{IV} at 70°C is about 60.

A deeper insight into the question of participation could probably be gained by comparison of the rates of *VIId* and *VIIId* with solvolysis rates of the correspond-

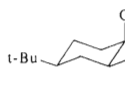
TABLE II

Comparison of Reaction Rates of Benzamido Methanesulphonates *Vd*—*VIIId* (k_{Mes}) with the "Corrected" Rates of Corresponding Stereoisomeric Tosylates *XIa*—*XIVa* (k_{Tos}) in Ethanol at 70°C

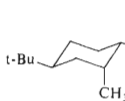
Compound	$k_{Mes} \cdot 10^5$	Compound[a]	$k_{Tos} \cdot 10^5$	$\frac{k_{Mes}}{1{\cdot}6k_{Tos}}$[b]
Vd	6·95	*XIa*	36·7	0·12
VId	21·8	*XIIa*	36·3	0·37
VIId	131	*XIIIa*	2·99	27·4
VIIId	23·3	*XIVa*	0·376	38·8

[a] Ref.[6]. [b] The factor 1·6 should compensate the higher reactivity of the methanesulphonyloxy group than the toluenesulphonyloxy group.

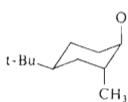
* The reaction rates of our methanesulphonates *Vd*—*VIIId* must be compared with the corresponding methanesulphonates *Xlb*—*XVIb* rather than tosylates *XIa*—*XVIa*. Since we did not prepare these compounds, we decided to "correct" the known[6] solvolysis rates of the tosylates *XIa*—*XVIa*. From some model measurements[11,12] it is known that the ethanolysis of mesylates is about 1·4—1·8 times faster than the same reaction of tosylates and we may therefore correct the rates accordingly, using arbitrarily the factor 1·6.



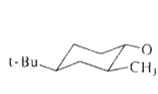
XI



XII

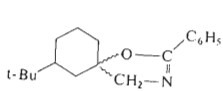


XIII



XIV

a, O = OTs
b, O = OMes



XXII

ing 4-tert-butyl-2-methylcyclohexyl toluenesulphonates *XIIIa*, *XIVa* (Table II). Thus, the ratios (corrected for the tosyl group, see footnote on p. 1452) of the rates of the "*trans*"-isomers are very similar, being for k_{VIIId}/k_{XIIIb} about 30 and for k_{VIIId}/k_{XIVb} about 40; in the 1,2-series[2] k_{IV}/k_{XIVb} (for the "diequatorial" epimers) is also about 40 whereas in the case of the "diaxial" compound *III* there is a very powerful enhancement of the reaction rate as compared with "plain" solvolysis, k_{III}/k_{XIIIb} being about 400. This indicates that in the "diaxial" 1,3-isomer *VIId* the acceleration due to neighbouring group participation is much smaller than in the corresponding 1,2-isomer *III*, and is almost the same as in the "diequatorial" isomer *VIIId*.

The respective values of k_H/k_{NO_2} for *VIId* and *VIIId* are 2·9 and 2·2, being thus substantially lower than the corresponding values in the 1,2-series[11] (about 4). This could be due to a lower degree of participation in the 1,3- as compared with the 1,2--series; however, since the cyclisation reactions in both series are different, this comparison may be only informative at best.

As can be seen from models, in the transition state in the "diaxial" derivative *VIId* it is not possible to achieve simultaneously planarity of the segment MesO—C... ...O=C—N—C and collinearity of the breaking and forming bonds O...C—OMes, an arrangement which is likely to be optimal for the cyclisation. On the other hand, this condition can be satisfied in the "diaxial" compound *III* in the 1,2-series. In the diequatorial isomer *VIIId* the chair-like transition state (Scheme 2, *E*) has a very favourable geometry, whereas neither of the alternative boat-like transition states in *VIIId* seems to be favourable enough to be able to compete with the chair transition state *E* depicted in Scheme 2 since in all of them either the tert-butyl group is in a crowded position or the geometry of the reaction site is unfavourable.

The almost same rate enhancement in the diaxial and diequatorial isomer *VIId* and *VIIId* as compared with the rate of *XIIIb* and *XIVb* seems to justify the as-

sumption that the geometry of the diaxial transition state in the 1,3-series is not very advantageous since if it were, the rate enhancement should be much greater in the biased diaxial isomer *VIId* than in the diequatorial one (*VIIId*). Consequently, if there is no energetic advantage in the diaxial transition state, there is no reason to suppose that the diequatorial isomer *VIIId* should react in a boat form with "quasi-diaxial" arrangement of the mesyl and benzamidomethyl groups (Scheme 2, *F*). Since, as mentioned above, other boat forms may be regarded as energetically very unfavourable, the chair-like transition state *E* in the cyclisation of the diequatorial isomer *VIIId* seems to be more probable than a boat-like form *F*.

The fact that the "diequatorial" isomer *VIIId* and the *cis*-isomer *VId* have very similar reaction rates (Table I) might be startling on a first sight, because of danger of a strong solvolytic contribution in the reaction of the former isomer. In actual fact, the situation is not so bad: if we compare the solvolysis rates in the 4-tert-butyl--2-methylcyclohexyl tosylate series[6], we see that the methyl-axial, tosyloxy-equatorial isomer *XIIa* solvolyses about 100 times faster than the diequatorial isomer *XIVa*.

There is no reason why not to transfer this relation to the compounds under study, and therefore the solvolysis of our "diequatorial" isomer *VIIId* should be also 100 times slower than that of the *cis*-isomer *VId*, *i.e.* it should amount to $21{\cdot}8 \times \times 10^{-5}/100 = 0{\cdot}22 \,.\, 10^{-5}$. Thus, a solvolytic reaction will not contribute significantly to the reaction of *VIIId*; this is in accord with the almost quantitative yields of the dihydrooxazine *Vf*. The same reasoning leads to an estimated rate of solvolysis of the "diaxial" derivative *VIId* ($0{\cdot}58 \times 10^{-5}$) which is obviously insignificant when compared with the actual reaction rate of this isomer (131×10^{-5}).

The concept of a chair-like transition state in *VIIId* evokes necessarily the question why the *cis*-isomer *VId* does not afford – by an intramolecular S_N2 reaction – also the dihydrooxazine. The likely explanation may be simply that the chair in the actual transition state of the *trans*-isomer *VIIId* is more or less flattened, whereas in the *cis*-isomer *VId* the reaction requires a (probably severe) puckering of the ring, a process regarded as energetically very demanding. The same reasoning holds for the *cis*-isomer *Vd*.

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[a] Prepared from the amino alcohol by the usual Schotten–Baumann procedure. [b] For $C_{18}H_{17}NO_2$ (289·4) calculated: 74·70% C, 9·40% H, 4·84% N. [c] For $C_{18}H_{26}N_2O_4$ (334·4) calculated: 64·65% C, 7·84% H, 8·38% N. [d] Prepared from the corresponding benzamide by treatment with methanesulphonyl chloride in pyridine; the product was not crystallised and the m.p.'s and analyses refer to crude compound. [e] For $C_{19}H_{29}NO_4S$ (367·5) calculated: 62·09% C, 7·96% H, 3·81% N. [f] For $C_{15}H_{21}NO_4S$ (311·2) calculated: 57·86% C, 6·80% H, 4·50% N. [g] For $C_{19}H_{28}N_2O_6S$ (412·5) calculated: 55·32% C, 6·84% H, 6·79% N. [h] For $C_{15}H_{20}N_2O_6S$ (356·3) calculated: 50·56% C, 5·66% H, 7·86% N.

TABLE III

Yields, Physical Constants and Analyses of Derivatives of 2-Aminomethyl-4-tert-butylcyclohexanols

Compound	Yield, %	M.p., °C (solvent)	Found		
			% C	% H	% N
N-Benzoyl Derivatives[a,b]					
Vb	88	186–187 (benzene)	74·39	9·50	4·71
VIb	86	151–152 (toluene)	74·89	9·53	4·97
VIIb	84	177–177·5	74·49	9·52	4·65
VIIIb	84	138–139	74·43	9·22	4·87
N-*p*-Nitrobenzoyl Derivatives[a,c]					
Vc	97	253–254 (toluene)	64·90	8·04	8·55
VIc	91	184 (70%) methanol)	64·61	7·90	8·31
VIIc	96	120–121·5 (ethanol)	64·67	8·06	8·63
VIIIc	67	223·5–224·5 (ethanol)	64·96	7·99	8·34
N-Benzoyl O-Methanesulphonyl Derivatives[d,e]					
Vd	87	60–62	62·70	8·24	3·58
VId	81	129–132	61·65	7·90	3·81
VIId	65	85–87	61·51	7·96	3·69
VIIId	92	91–96	62·67	7·84	3·50
IXd	75	98–100	60·52[f]	7·13[f]	4·45[f]
Xd	98	120–121	57·15[f]	6·68[f]	4·32[f]
N-*p*-Nitrobenzoyl O-Methanesulphonyl Derivatives[d,g]					
Ve	81	117–119	56·36	7·10	6·94
VIe	86	152–154	55·75	7·23	6·49
VIIe	91	109–111	55·88	6·93	6·48
VIIIe	89	129–131	54·44	6·98	6·23
IXe	68	105–106	49·74[h]	5·64[h]	7·81[h]
Xe	98	126–127	51·00[h]	5·64[h]	7·84[h]

EXPERIMENTAL

trans-2-Aminomethylcyclohexanol (*Xa*) was synthesized starting from the lactone of *trans*-2-carboxymethylcyclohexanol[13] which was transformed into the amino alcohol by Curtius degradation of the corresponding hydrazide. The *cis*-2-aminomethylcyclohexanol (*IXa*) was prepared *via* dihydrooxazine from the *trans*-benzamide *Xb* by treatment with thionyl chloride, essentially as described by Mousseron and collaborators[14]. The properties of the bases as well as their N-benzoyl and N-*p*-nitrobenzoyl derivatives agreed well with the constants given recently by Bernáth and coworkers[15].

cis-5-tert-Butyl-*cis*-2-hydroxycyclohexanecarboxamide (*XVI*)

This compound, m.p. 161—162°C, was prepared in 89% yield from the methyl ester of the acid *XV* (ref.[7]) by treatment with methanolic ammonia (saturated at 0°C) at 100°C in an autoclave. For $C_{11}H_{21}NO_2$ (199·3) calculated: 66·29% C, 10·62% H, 7·03% N; found: 66·39% C, 10·66% H, 7·10% N.

cis-2-Aminomethyl-*cis*-4-tert-butylcyclohexanol (*Va*)

The amide *XVI* (3·0 g) was added in parts to a stirred solution of lithium aluminium hydride (1·7 g) in tetrahydrofuran (50 ml), the mixture refluxed for 7 hours, cooled and treated with water (5 ml) followed by 20% sodium hydroxide (8 ml). The precipitated hydroxides were filtered off and washed with hot tetrahydrofuran and ether. The combined filtrates were taken down and treated with aqueous hydrochloric acid, the solution extracted with ether and taken to dryness, yield 3·2 g (96%) of the hydrochloride, m.p. 271—273°C (ethanol–ether). For $C_{11}H_{24}ClNO$ (221·8) calculated: 59·57% C, 10·91% H, 6·32% N; found: 59·28% C, 10·91% H, 6·32% N. The amino alcohol *Va* was liberated by potassium hydroxide, m.p. 69—70°C. For $C_{11}H_{23}NO$ (185·3) calculated: 71·30% C, 12·51% H, 7·56% N; found: 71·19% C, 12·42% H, 7·65% N.

cis-2-Aminomethyl-*trans*-4-tert-butylcyclohexanol (*VIa*)

A solution of *trans*-4-tert-butyl-*cis*-2-methanesulphonyloxymethylcyclohexanol[8] (*XVII*) (9·25 g) in dimethylformamide (250 ml) was treated with sodium azide (35 g) in water (75 ml), the solution heated for 4 hours to 95°C, diluted with water (1 liter) and the product taken up into light petroleum. The extracts were washed with saturated sodium chloride solution, dried over sodium sulphate and the solvent distilled off. The residue consisting of the crude azide (7·0 g, 94%) and melting at 60—65°C was dissolved in ether (50 ml) and treated under cooling with a solution of lithium aluminium hydride (3·5 g) in ether (100 ml). The mixture was refluxed for 2 hours, cooled and decomposed with water and 15% sodium hydroxide. The precipitate was filtered off, washed three times with ether, and the filtrate treated with excess ethereal hydrogen chloride, giving 4·7 g (60%) of the hydrochloride, m.p. 235—240°C. For $C_{11}H_{24}ClNO$ (221·8) calculated: 59·60% C, 10·90% H, 6·32% N; found: 59·47% C, 10·80% H, 6·19% N. The free base melted at 76—78°C (subl.). For $C_{11}H_{23}NO$ (185·3) calculated: 71·30% C, 12·51% H, 7·56% N; found: 71·50% C, 12·43% H, 7·52% N.

trans-5-*tert*-Butyl-*trans*-2-hydroxycyclohexaneacetic Acid (*XIX*)

cis-4-tert-Butyl-1,2-epoxycyclohexane[7] (*XVIII*) (23 g) was allowed to react with diethyl sodiomalonate (50% excess)in ethanol[16]. The crude diester was refluxed with 10% aqueous sodium

hydroxide and the resulting crude dicarboxylic acid was heated for 15 min in pyridine at the reflux yielding 24 g (75%) of the acid *XIX*, m.p. 158–159°C (ethyl acetate). For $C_{12}H_{22}O_3$ (214·3) calculated: 67·25% C, 10·35% H; found: 67·14% C, 10·31% H.

trans-2-Aminomethyl-*cis*-4-tert-butylcyclohexanol (*VIIa*)

The acid *XIX* on treatment with diazomethane afforded the ester, b.p. 126–129°C/0·3 Torr, in quantitative yield. For $C_{13}H_{24}O_3$ (228·3) calculated: 68·38% C, 10·59% H; found: 68·34% C, 10·23% H. The hydrazide was prepared by refluxing the ester (25 g) and 60% hydrazine hydrate (15 ml) in ethanol (50 ml) for 4 hours; m.p. 175–176°C (ethanol), yield 19 g (77%). For C_{12}·$.H_{24}N_2O_2$ (228·3) calculated: 63·24% C, 10·49% H, 12·06% N; found: 63·12% C, 10·60% H, 12·27% N;. A solution of the hydrazide (15 g) in 0·5M-HCl (200 ml) was treated under cooling with a 10% aqueous solution of sodium nitrite (60 ml). The mixture was extracted with ether and the extracts dried over magnesium sulphate at 0°C for one hour. Ethanol (300 ml) was added to this solution of the azide and the ether and ethanol distilled off. The residue, which consisted of the crude urethane, was refluxed for 5 hours with 15% aqueous potassium hydroxide (100 ml). The mixture was acidified, extracted with ether and the aqueous layer made alkaline (KOH). The product was taken up into ether. The usual work-up procedure gave 8·0 g (66%) of the base *VIIa*, m.p. 103–104°C (ether, pressure). For $C_{11}H_{23}NO$ (185·3) calculated: 71·30% C, 12·51% H, 7·56% N; found: 71·51% C, 12·68% H, 7·32% N.

TABLE IV

Physical Constants and Analyses of Dihydrooxazines *Vf*–*VIIIf* and their Picrates

Compound	Method[a]	M.p., °C	Found		
			% C	% H	% N
		Dihydrooxazines[b]			
Vf	A, B	102–103	79·67	9·28	5·10
VIf	A, B	135–136	79·59	9·38	5·12
VIIf	A	75·5–76·5	79·65	9·40	5·25
VIIIf	A	119–120	80·04	9·21	5·19
		Picrates[c,d]			
Vf	—	173–174·5	57·67	5·70	11·24
VIf	—	206–208	57·73	5·92	11·20
VIIf	—	159–161	57·39	5·61	11·40
VIIIf	—	209–210	57·31	5·56	11·36

[a] A, preparation from the corresponding amino alcohol by treatment with ethyl benzimidate, **B**, preparation by inversion of the epimeric methanesulphonate. [b] For $C_{18}H_{25}NO$ (271·4) calculated: 79·66% C, 9·29% H, 5·16% N. [c] The number given denotes the corresponding dihydrooxazine. [d] For $C_{24}H_{28}N_4O_8$ (500·5) calculated: 57·59% C, 5·64% H, 11·20% N.

cis-5-Tert-butyl-*trans*-2-hydroxycyclohexanecarboxamide (*XXI*)

A solution of *cis*-5-tert-butyl-*trans*-2-hydroxycyclohexanecarboxylic acid (*XX*) (3 g) and N-ethylpiperidine (1·7 g) was treated at −2°C with an equivalent of sec-butyl chloroformate. The mixture was allowed to stand at −2°C for about 15 minutes, treated with a solution of ammonia (about 10% excess) in chloroform, kept at −2°C for about 45 min and refluxed until no more carbon dioxide was evolved. The chloroform was distilled off under reduced pressure, the residue treated with a saturated sodium hydrogen carbonate solution, the crystalline product filtered off, washed with water and ethanol, yield 2·1 g (70%), m.p. 209° (ethanol). For $C_{11}H_{21}NO_2$ (199·3) calculated: 66·29% C, 10·62% H, 7·03% N; found: 66·42% C, 10·53% H, 7·03% N.

TABLE V

First Order Rate Constants, k, for the Reaction of the Methanesulphonyl Derivatives in the Presence of Potassium Acetate in Ethanol[a]

Compound	$k \cdot 10^5$, s^{-1} (t, °C)			
Vd	2·09 (60·02°)	7·00 (70·01°)	21·7 (80·00°)	—
Ve	1·83 (60·02°)	5·63 (70·01°)	16·9 (80·00°)	46·0 (90·03°)
VId	1·99 (49·92°)	6·81 (60·02°)	21·8 (70·01°)	64·8 (80·00°)
VIe	1·25 (49·92°)	4·47 (60·02°)	15·1 (70·01°)	44·5 (80·00°)
VIId	4·73 (39·90°)	15·6 (49·92°)	45·6 (60·02°)	—
VIIe	5·78 (49·92°)	17·0 (60·02°)	45·1 (70·01°)	—
VIIId	2·38 (49·92°)	7·85 (60·07°)	24·1 (70·17°)	—
VIIIe	3·49 (60·02°)	3·51 (60·07°)	10·7 (70·01°)	30·0 (80·00°)
IXd	1·32 (60·02°)	4·85 (70·01°)	15·3 (80·00°)	—
IXe	1·33 (60·02°)	4·86 (70·01°)	14·8 (80·00°)	43·4 (90·03°)
Xd	3·06 (49·92°)	8·89 (60·02°)	24·7 (70·01°)	—
Xe	3·79 (60·02°)	11·9 (70·01°)	33·8 (80·00°)	—

[a] The kinetic measurements were carried out as described for the 1,2-derivatives in Parts XIII and XX of this series (ref.[1,2]).

trans-2-Aminomethyl-*trans*-4-tert-butylcyclohexanol (*VIIIa*)

The amide *XXI* (1·3 g) was reduced as described for its epimer *XVI*, yield of the crude hydrochloride 1·2 g (83%); this was used directly for further work. The base liberated from the hydrochloride had b.p. 128–131°C/2 Torr, m.p. 80–81°C. For $C_{11}H_{23}NO$ (185·3) calculated: 71·30% C, 12·51% H, 7·56% N; found: 71·13% C, 12·64% H, 7·64% N.

Dihydrooxazines *Vf*– *VIIIf*

These compounds were prepared in 80–90% yield by heating the corresponding amino alcohol with ethyl benzimidate to 110–120°C for 6 hours[9]. The crude product was purified by chromatography on an alumina column (activity II) and sublimation. Elemental analyses and physical constants of dihydrooxazines and their picrates are listed in Table IV.

Cyclisation of *trans*-2-Benzamidomethyl-*cis*-4-tert-butylcyclohexyl Methanesulphonate (*VIId*)

A. A solution of the methanesulphonate *VIId* (1·0 g) and fused potassium acetate (0·38 g) in ethanol (150 ml) was heated to 110°C for four hours in an autoclave. The mixture was taken down, the residue shaken between sodium carbonate solution and ether, the ethereal layer dried and the solvent evaporated, leaving 0·72 g (98%) of the dihydrooxazine, m.p. 134–136°C, identical (mixed m.p., IR-spectrum) with an authentic specimen of *Vlf* prepared from *VIa*.

B. A solution of the benzamide *VIIb* (4·0 g) in thionyl chloride (16 ml) was allowed to stand overnight, the excess thionyl chloride was distilled off and the residue shaken between ether and a potassium carbonate solution. The ethereal layer was dried, and taken down, affording 3·6 g (96%) of crystals, m.p. 133–135°C, identical with the authentic dihydrooxazine *Vlf*.

Cyclisation of *trans*-2-Benzamidomethyl-*trans*-4-tert-butylcyclohexyl Methanesulphonate (*VIIId*)

The benzamide *VIIId* (1·8 g) was heated with fused potassium acetate (0·6 g) in ethanol (200 ml) to 90°C for 3 hours in an autoclave and the mixture was worked up as described for *VIId*. The yield of dihydrooxazine *Vf* was 1·3 g (98%), m.p. 100–101°C. The product was identical with the dihydrooxazine prepared from the amino alcohol *Va*.

cis-2-Benzamidomethyl-*cis*-4-tert-butylcyclohexanol (*Vb*)

A mixture of the dihydrooxazine *Vf* (1·3 g) and 10% hydrochloric acid (25 ml) was boiled for 15 min, evaporated, dissolved in water, extracted with ether and the aqueous layer poured into an excess of 10% aqueous sodium hydroxide. The separated crystals were crystallised from benzene, giving 0·7 g (36%) of the benzamide, m.p. 186–187°C, which was identical with authentic *Vb* obtained from the amino alcohol *Va*.

Ethanolysis of *Vd*

A solution of *Vd* (921 mg, 2·5 mmol) and freshly fused potassium acetate (312 mg, 3·2 mmol) in ethanol (150 ml) was heated to 95°C for 7 hours. The mixture was taken to dryness and the residue shaken between ether and 1% aqueous sodium hydroxide. The ethereal layer was treated with a solution of picric acid (200 mg) in ether (40 ml) and after one hour the separated picrate filtered off, washed with ether and dried, yield of *XXII* 75 mg (6%), m.p. 189–190°C. For C_{24}-

$.H_{28}N_4O_8$ (500·5) calculated: 57·59% C, 5·64% H, 11·20% N; found: 57·60% C, 5·67% H, 11·28% N. The base, liberated from the picrate by lithium hydroxide solution, was an oil, *m/e* 271. NMR-spectrum (CCl_4): 0·88 s (9H) t-C_4H_9, 1·00–2·10 m (9 H) 4× CH_2 + t-C_4H_9—C—H, 3·73 s (2 H) —CH_2—N, 7·30–7·50 and 7·90–8·00 m (5 H) aromatic protons (Table V).

The ethereal mother liquors from the precipitated picrate were washed several times with an aqueous lithium hydroxide solution, dried and taken down. Chromatography of the oily residue on silica gel (100 g) afforded two main fractions (eluant pentane–ether 1 : 1). 1st fraction oil (481 mg, 71%), *m/e* 271, NMR-spectrum (CCl_4): 0·97 s (~9 H) tert-C_4H_9, 1·0–2·30 complex m (~7 H) 3× CH_2 + CH, 3·95 d (~2 H) —CH_2—NH, 5·62 m (~1 H) vinylic proton, 6·46 broad m (~1 H), 7·26–7·55 and 7·70–7·90 m (~5 H) phenyl. IR-spectrum (CCl_4), cm^{-1}: 1366, 1393 (t-C_4H_9), 1487, 1578, 1603, 3030, 3060 (aromatic ring), 1658 (amide CO), 1517 (δN—H), 3335, 3450 (νN—H). The data show that the fraction represents impure 3-benzamidomethyl-1-tert-butyl-3-cyclohexene. 2nd fraction (121 mg, 12%) was an oil, *m/e* 331, IR-spectrum (CCl_4), cm^{-1}: 1366, 1393 (t-C_4H_9), 1487, 1580, 1603, 3030, 3060 (aromatic ring), 1528, 1648 (amide), 1258, 1717, sh 1735 (acetate). The NMR spectrum indicates a mixture of several compounds, probably of isomeric acetoxy-benzamidomethyl-tert-butylcyclohexanes.

Ethanolysis of *VId*

This isomer (459 mg, 1·3 mmol) was solvolysed under the same conditions as *Vd*. The treatment of the reaction product with ethereal picric acid gave no precipitate. Chromatography afforded as the first fraction an oil (231 mg, 68%) which had the same NMR and IR spectrum as had the first fraction in the solvolysis of *Vd*. This fraction is also mainly 3-benzamidomethyl-1-tert-butyl--3-cyclohexene. The further two fractions (10 mg, 2·4%, and 52 mg, 12%) were shown (IR, NMR) to be mixtures containing mainly acetates. No fraction gave a picrate.

Stability of Dihydrooxazines under Reaction Conditions

A solution of dihydrooxazine (50 mg) and dry potassium methanesulphonate (20 mg) in ethanol (10 ml) containing 0·130 ml of glacial acetic acid, was heated in a sealed ampoule to 95°C for 10 hours. The mixture was worked up as described for the reaction of benzamidomethanesulphonate *VIIId*. In all cases the starting dihydrooxazine was recovered in high yield and no other compounds were detected by thin layer chromatography of the product.

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