DIEQUATORIAL CHAIR TRANSITION STATE IN CYCLISATION OF A DIEQUATORIAL BENZAMIDO METHANESULPHONATE*

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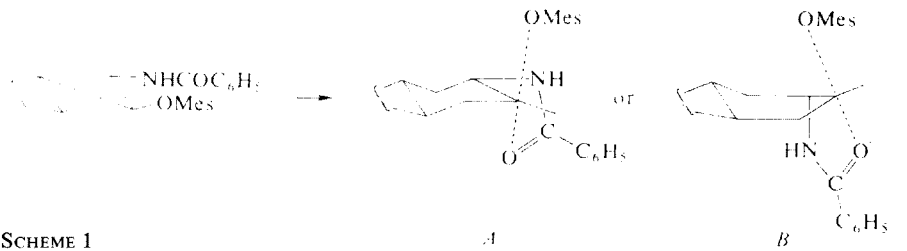
The reaction of *cis*-4-benzamido-*trans*-5-methanesulphonyloxy-*trans*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene (in which both functional groups are equatorial) in ethanol affords the corresponding Δ^2-oxazoline in quantitative yield. Since this system cannot react *via* diaxial boat form, the oxazoline formation represents the direct proof of a (distorted) chair transition state with the functional groups reacting in equatorial positions.

In our preceding paper[1] we studied the kinetics of the cyclisation reaction of N-benzoyl-O-methanesulphonyl derivatives of 2-aminocyclohexanols in which both functional groups occupy an equatorial position. The comparison of reaction rates of variously substituted conformationally biased compounds indicated that the formation of Δ^2-oxazolines might proceed *via* a "flattened chair" transition state (Scheme 1, *A*), in which both groups are "pseudoequatorial", rather than *via* a boat form (Scheme 1, *B*) with a "pseudodiaxial" arrangement (previously[2] considered to be the only possible transition state). This result was based mainly on the assumption that a substituent in a boat form should strongly affect the reaction rate whereas in the flattened chair form a remote substituent should have no great influence. There has been, of course, no direct proof that a transition state like the diequatorial chair form (*A*) really can exist and therefore any progress in this direction was highly desirable.



SCHEME 1 *A* *B*

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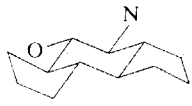
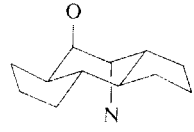
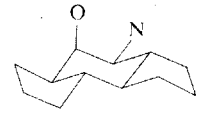
Some time ago we synthesized derivatives of the *trans*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene system[3]. This system is completely rigid, holding the six-membered ring in an almost ideal chair form. As seen on models, this ring can flip neither into another chair nor into a boat form. Therefore, if the diequatorial derivative *Id* (Scheme 2) affords by S_N2 reaction the corresponding oxazoline *IV*, the reaction must proceed *via* the diequatorial chair transition state. We therefore set out to synthesize the stereoisomeric amino alcohols *Ia*–*IIIa* and to study the rates and the outcome of the reactions of their derivatives.



I



II

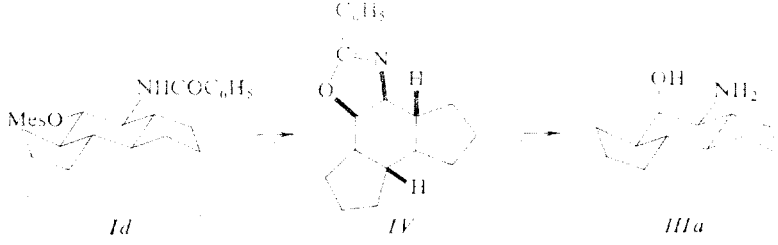


III

a; O = OH, N = NH_2 *b*; O = OH, N = $NHCOC_5H_6$ *c*; O = OH, N = $NHCOC_6H_4$-*p* (NO_2) *d*; O = OMes, N = $NHCOC_6H_5$ *e*; O = OMes, N = $NHCOC_6H_4$-*p*(NO_2)

Synthesis and Assignment of Configuration

For the synthesis of the diequatorial isomer *Ia* we chose the route, starting from the ketone *V*, *via* the keto acid *VI* (Scheme 3). However, the realisation of this route encountered some difficulties. As already reported[3], ketone *V* smoothly epimerises to give its *cis*-3a,8b isomer, and even a brief treatment of *V* with triphenylmethyl potassium in ether at 0°C (conditions required for carboxylation) resulted in its extensive epimerisation. The method of choice appeared to be the carboxylation of lithium enolate of *V*. This method makes use of the finding that, unlike other alkali metal enolates, lithium enolates of α-alkyl ketones undergo only slow proton transfer reaction on the α-carbon and hence the epimerisation of the α-alkyl is considerably



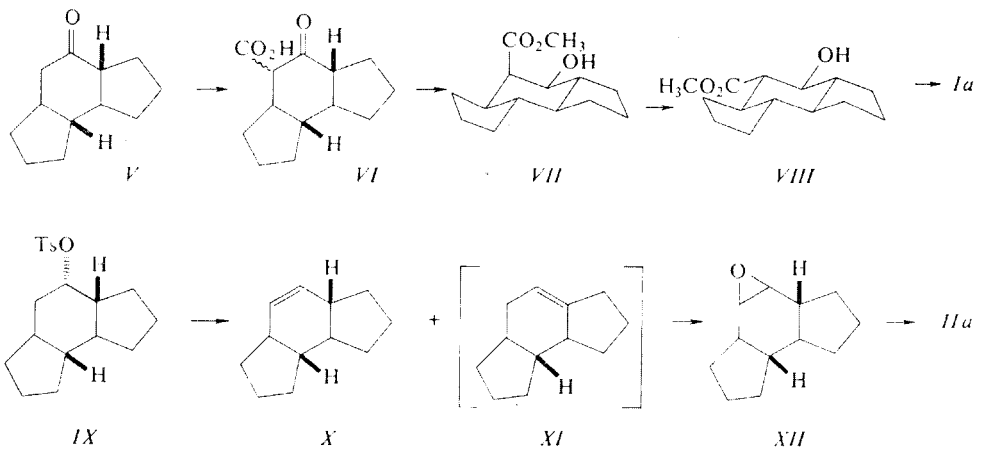
Id *IV* *IIIa*

SCHEME 2

suppressed[4-6]. In fact, carboxylation of *V* using triphenylmethyllithium in dimethoxyethane at −10°C, followed by immediate reduction of the keto acid salt with sodium borohydride, was not accompanied by epimerisation of the system and afforded the hydroxy ester *VII*. This was equilibrated to the desired diequatorial isomer *VIII* which was transformed into *Ia* by Curtius degradation. The *cis*-isomer *IIIa* was prepared from *Id* by inversion procedure *via* the oxazoline *IV*.

For the diaxial amino alcohol *IIa* the starting compound was the olefin *X*. This was synthesized from the toluenesulphonate *IX* (ref.[3]) by reaction with potassium tert-butoxide and subsequent separation from the simultaneously arising isomeric olefin *XI* by gas liquid chromatography. The structure of *X* was proved by NMR spectroscopy. The olefin *X* was transformed into the epoxide *XII* which was subjected to ammonolysis to give the amino alcohol *IIa*. The configuration of the amino alcohols *Ia* and *IIa* was confirmed by comparison of the coupling constants in the NMR spectra of the methyl esters *VII* and *VIII* and of the N-benzoyl-O-methanesulphonyl derivatives *Id* and *IId*. The observed coupling constants are depicted in Fig. 1. It is evident that their values determine unequivocally the configuration of the compounds in question.

Also the IR-spectroscopic measurements of the hydrogen bond in the amino alcohols *Ia*, *IIa* and *IIIa* fully support the configurational assignment: in the 3 μ region *Ia* exhibits a bonded hydroxyl band at 3527 cm^{-1} ($\Delta\nu$(OH) = 106 cm^{-1}), which is generally found at this position in 2-aminocyclohexanols with both functional groups in equatorial position[7]. The spectrum of *IIa*, as well as its N,N-dimethyl derivative, contains only a free hydroxyl band at 3630 cm^{-1}, in agreement with the



SCHEME 3

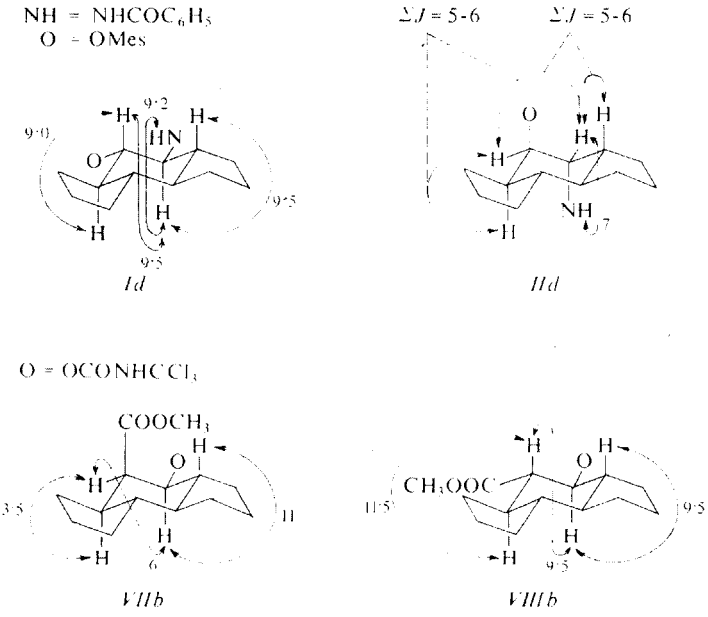
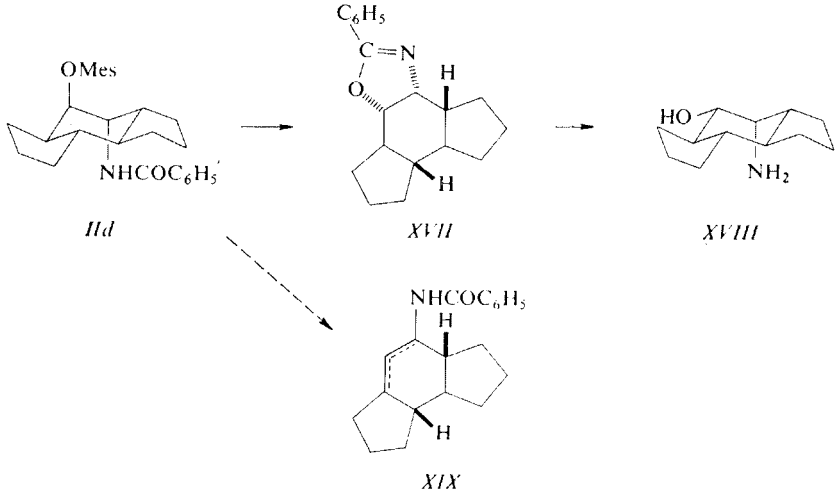


FIG. 1

The Coupling Constants Taken from the NMR Spectra of *Id*, *IId*, *VII* and *VIII*

Varian HA-100; *VII* and *VIII* were measured in $CDCl_3$ as trichloroacetylurethanes made *in situ* by treatment with trichloroacetyl isocyanate; *Id* and *IId* measured in hexadeuteriodimethyl sulphoxide.



SCHEME 4

axial position of both functional groups. As expected, the bonded hydroxyl band of *IIIa* is located at 3492 cm^{-1} confirming thus its *cis* configuration ($\Delta\nu$(OH) = = 145 cm^{-1}).

Rate Studies

The reaction rates (in ethanol at 70°C) of all measured compounds are listed in Table I. The reaction of the diaxial derivative *IId* gives about 92% of the corresponding oxazoline *XVII*, the remainder being products of elimination (unsaturated derivatives, presumably *XIX*) (Scheme 4). The rate of solvolysis of *IId* is thus only about ten times lower than the rate of the cyclisation reaction. The diequatorial isomer *Id* affords the oxazoline *IV* as the sole product in quantitative yield. The reaction rate is about 15 times lower than that of the diequatorial *trans*-decalin derivative[1] (*XIII*). This effect may be ascribed to the inherently lower reactivity of the perhydro-*as*-indacene system, since the rate of the diaxial derivative *IId* is also lower (about 20 times) than the rate of the corresponding decalin derivative *XIV*. Interestingly enough, the $\Delta S^{\neq}$ value of the reaction of the diequatorial isomers *Id* and *Ie* is positive whereas all other compounds studied exhibit a negative value of entropy. This feature might be due to the great rigidity of the tricyclic system.

Since, as already mentioned[3], the perhydro-*as*-indacene system does not allow the six-membered ring to adopt a boat form, the compound *Id* must react *via* the "diequatorial chair" transition state. If the lower reactivity of *Id* is indeed due to the lower reactivity of the system as such, then the transition state in *Id* is probably similar to that of the diequatorial monocyclic or decalin derivatives studied in our previous

TABLE I

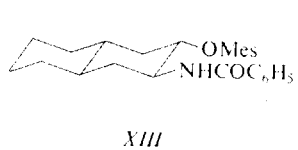
First Order Rate Constants, k_{70}, of the Reaction of the Derivatives of the Amino Alcohols *Ia*—*IIIa*, *XII* and *XIII* at 70°C in Ethanol, Values of k_H/k_{NO_2} and Values of the Thermodynamic Parameters

Compound	$10^5\, k_{70}$	k_H/k_{NO_2}	$\Delta H^{\neq}$	$\Delta S^{\neq}$
Id	0·785[a]	5·9[a]	29·3	+3
Ie	0·133[a]		32·9	+10
IId	63·6	3·06	24·2	−3
IIe	20·8		25·0	−3
IIId	1·62	1·1	[b]	[b]
IIIe	1·50		[b]	[b]
XIII[c]	12·2	3·6	23·8	−7·5
XIV[c]	1 300[a]	3·9[a]	22·5	−2·0

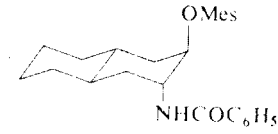
[a] Extrapolated from data at lower temperatures; [b] measured only at 70°C; [c] ref.[1].

paper[1]. In other words, if *Id* reacts *via* a chair transition state, then also other diequatorial benzamido methanesulphonates (*e.g. XIII*) may react *via* this form.

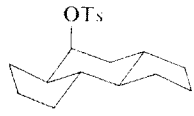
There is in principle an alternative (though unlikely) way how *Id* could cyclise to the oxazoline. This route involves an S_N1 reaction on the carbon, carrying the



XIII



XIV



XV

XVI

methanesulphonyloxy group. At first sight, the fact that the *cis*-isomer *IIId* reacts twice as fast as *Id* might speak in favour of the possibility of an S_N1 mechanism in the reaction of *Id*. The velocity of an S_N1 reaction in *Id* can be estimated on the basis of solvolysis rates of the epimeric tosylates *XV* and *XVI*. The equatorial tosylate *XVI* reacts (in 70% ethanol) 360 times slower than the axial isomer *XV* (ref.[8]): we may therefore expect an S_N1 reaction in *Id* to be also very sluggish. Therefore the intramolecular S_N2 cyclisation should be far preferred in this isomer.

Also the comparison of the values of k_H/k_{NO_2} (where k_H is the rate of benzamido- and k_{NO_2} the rate of *p*-nitrobenzamido methanesulphonate) makes this possibility improbable. As discussed earlier[9,10] this value of k_H/k_{NO_2} is regarded as indicative of the extent of participation of the benzamido group in the cyclisation reaction: the greater the participation, the higher is this value. The value k_H/k_{NO_2} for *II* is about 3·3 and for *I* 5·9 (at 70°C), whereas for the *cis*-isomer *III* it is only 1·1.

We may therefore conclude that the cyclisation of the tricyclic diequatorial derivative *Id* represents the first direct evidence of the diequatorial chair transition state in this reaction.

EXPERIMENTAL

Kinetic Measurements

The kinetic procedure was the same as reported previously[11], except that only 0·15 mmol of benzamido methanesulphonate was used in a kinetic run. The experimental rate constants are listed in Table III.

trans-8a-*transoid*-8a,8b-*trans*-8b-1,2,3,3a,5a,6,7,8,8a,8b-Decahydro-*as*-indacene (*X*)

A solution of crude tosylate *IX* (44·6 g, prepared directly from the crude reduction product of 3a,4-epoxy-*cis*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene[3]) in 1M potassium tert-butoxide in tert-butyl alcohol (300 ml) was heated under reflux for 2·5 hours. The reaction mixture was diluted with water, extracted with pentane, the organic layer washed with water, passed through short silica gel column and the solvent distilled off, leaving a mixture of *X* and *XI* (3 : 2), b.p. 104–105°C/11 Torr (17·5 g). Preparative gas liquid chromatography (1,2,3-tris (2-cyanoethoxy)-propane) afforded pure *X*, b.p. 96°C/15 Torr, m.p. 20–21°C (in bulk), yield 3·3 g (37%). NMR spectrum: 5·74 and 5·73 s (2 H) olefinic protons. For $C_{12}H_{18}$ (162·3) calculated: 88·82% C, 11·18% H; found: 89·13% C, 11·16% H.

4,5-Epoxy-*trans*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene (*XII*)

3-Chloroperoxybenzoic acid (0·6 g) was added in the course of 10 minutes to a solution of *X* (0·5 g) in dichloromethane (10 ml) under stirring and cooling. After 2 hours' standing at room temperature the epoxide was isolated in the usual manner, b.p. 122–123°C/15 Torr, m.p. 46 to 47°C, yield 0·4 g. For $C_{12}H_{18}O$ (178·3) calculated: 80·85% C, 10·18% H; found: 81·15% C, 9·90% H.

trans-4-Amino-*cis*-5-hydroxy-(*r*-3aH)-*trans*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene (*IIa*)

A mixture of *XII* (540 mg), ethanolic ammonia (saturated at 0°C, 40 ml) and few drops of a saturated aqueous ammonium chloride was heated in an autoclave to 130°C for 8 hours. The usual work-up procedure afforded 370 mg of *IIa*, m.p. 134–135°C. IR spectrum (C_2Cl_4, $5 \cdot 10^{-3}$M): 3630 cm^{-1} (OH), 3398 cm^{-1} (NH). For $C_{12}H_{21}NO$ (195·3) calculated: 73·80% C, 10·84% H, 7·17% N; found: 74·04% C, 10·88% H, 7·17% N. N,N-Dimethyl derivative, boiling at 110 to 120°C/0·2 Torr (bath) was prepared from *IIa* by Clarke-Eschweiler procedure in 75% yield. IR spectrum (C_2Cl_2, $5 \cdot 10^{-3}$M): 3630 cm^{-1}. For $C_{14}H_{25}NO$ (223·4) calculated: 75·28% C, 11·28% H, 6·27% N; found: 75·19% C, 11·08% H, 6·14% N.

Equilibration of *V* by Triphenylmethyl Potassium

A) A solution of *V* (178 mg, 1 mmol) in ether (5 ml) was added rapidly to a stirred suspension of triphenylmethylpotassium (1 mmol) in ether (10 ml) at −10°C. The mixture became colourless in about 30 seconds and was immediately decomposed by addition of dilute hydrochloric acid. The ethereal layer was washed twice with water, dried and taken down. Since the remaining mixture of ketones (together with triphenylmethane) could not be analysed as such, the residue was dissolved in ether, reduced with lithium aluminium hydride (100 mg in 4 ml of ether) and after the usual work-up procedure analysed by gas liquid chromatography. This analysis showed that the ketone mixture contained 50% of the epimeric ketone.

B) Triphenylmethyllithium was prepared by addition of ethereal 1M phenyllithium solution (0·29 ml) to a solution of triphenylmethane (72 mg, 0·295 mmol) in 1,2-dimethoxyethane (1 ml, distilled from lithium aluminium hydride) under nitrogen. The mixture was stirred for 2 hours at room temperature, cooled to 0°C and titrated with a solution of *V* (40 mg, 0·22 mmol) in ether (0·5 ml). The colourless mixture was stirred for 1 minute, decomposed with dilute hydrochloric acid, shaken between pentane and water, dried and taken down. The remaining ketones were reduced and analysed as described under *A*). Only about 2% epimerisation was found.

TABLE II

Physical Properties, Yields and Analytical Values of Derivatives of the Amino Alcohols *Ia*—*IIIa*

Compound	Yield %	M.p., °C (solvent)	Found		
			% C	% H	% N
		N-Benzoyl derivatives[a,b]			
Ib	92	252[c]	76·30	8·41	4·16
IIb	85	178—179 (benzene)	76·27	8·50	4·39
IIIb	86	208—209 (ethanol)	76·45	8·50	4·89
		N-*p*-Nitrobenzoyl derivatives[a,d]			
Ic	90	282—282·5[c]	65·91	7·17	8·13
IIc	89	263—263·5[c]	66·41	7·02	8·18
IIIc	89	230—232 (aq. ethanol)	64·62	6·94	7·98
		N-Benzoyl-O-methanesulphonyl derivatives[e,f]			
Id[h]	94	191—191·5 (ethyl acetate)	63·88	7·23	3·97
IId[i]	92	126—127[c]	64·12	7·29	3·87
IIId	89	178—178·5 (ethyl acetate)	63·94	7·34	3·79
		N-*p*-Nitrobenzoyl-O-methanesulphonyl derivatives[e,g]			
Ie	86	203·5—204[c]	56·75	6·24	6·71
IIe	90	146—148 (ethyl acetate)	57·00	6·15	6·73
IIIe	76	164—165[c]	56·48	6·30	5·68

[a] Prepared by the standard Schotten–Baumann procedure; [b] for $C_{19}H_{25}NO_2$ (299·4) calculated: 76·22% C, 8·42% H, 4·68% N; [c] crude compound; [d] for $C_{19}H_{24}N_2O_2$ (344·4) calculated: 66·26% C, 7·02 OH, 8·13% N; [e] prepared by treatment with methanesulphonyl chloride in pyridine; [f] for $C_{20}H_{27}NO_4S$ (377·4) calculated: 63·65% C, 7·21% H, 3·71% N; [g] for $C_{20}H_{26}N_2O_2S$ (422·4) calculated: 56·75% C, 6·20% H, 6·63% N, [h] NMR-spectrum (hexadeuteriodimethyl sulfoxide, tetramethylsilane): 2·89 s (3 H) CH_3, 4·06q (1 H) —C<u>H</u>—N, $J_{CH,NH}$ = 9·2 Hz, $J_{4,5}$ = $J_{3a,4}$ = = 9·5 Hz; 4·61 t (1 H) C<u>H</u>—O, $J_{4,5}$ = 9·5 Hz, $J_{5,5a}$ = 9·0 Hz; 7·30—7·50 m (5 H) aromatic H; 8·32 d (1 H) NH, $J_{NH,CH}$ = 9·2 Hz. (Fig. 1), [i] NMR-spectrum (hexadeuteriodimethyl sulfoxide, tetramethylsilane): 3·30 s (3 H), CH_3; 4·56 broad d (1 H) C<u>H</u>—N, $J_{CH,NH} \approx 7$ Hz, $J_{4,5}$ + + $J_{3a,4} \approx 5-6$ Hz; 4·79 broad s (1 H) C<u>H</u>—O, $J_{4,5} + J_{5,5a} \approx 5-6$ Hz; 7·30—7·55 m, 7·70—7·90 m (6 H) aromatic H + NH (Fig. 1).

trans-5-Hydroxy-*cis*-4-methoxycarbonyl-(*r*-3aH)-*trans*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene (*VIII*)

An ethereal 0·97M solution of phenyllithium (28 ml) was added to a solution of triphenylmethane (7·2 g, 29·5 mmol) in 1,2-dimethoxyethane (40 ml, distilled from lithium aluminium hydride under nitrogen), the mixture was stirred under nitrogen for 2 hours, cooled to 0°C and a solution of *V* (4·0 g) in ether (20 ml) was added dropwise. The yellowish mixture was immediately poured over solid CO_2, extracted with ice-cold 1% sodium hydroxide and the extracts poured immediately into a solution of sodium borohydride (4·0 g) in water (50 ml) and set aside overnight. The whole procedure was carried out as rapidly as possible. The separated salts were filtered, washed thoroughly with ether, the filtrate was extracted with ether (3x) and combined with the filtered salts on the filter. The slurry was made acid with concentrated hydrochloric acid and the mixture was extracted continuously with ether for 10 hours, affording 4·5 g of crystalline mixture of acids. This was dissolved in methanol, esterified with diazomethane, the solvents evaporated and the residue crystallized from light petroleum, affording 1·5 g of *VII*, m.p. 111–112°C. Chromatography of the mother liquors on a silica gel column (200 g, pentane–ether 1 : 1) gave another 0·9 g of *VII*, raising the yield to 2·4 g (45%, based on *V*). NMR spectrum ($CDCl_3$, tetramethylsilane and trichloroacetyl isocyanate): 3·42 dd (1 H), $J = 6$ Hz, $J = 3·5$ Hz, C<u>H</u>COOCH$_3$; 3·67 s (3 H) COOCH$_3$; 4·90 q (1 H) $J = 17$ Hz, splittings 6 and 11 Hz, C<u>H</u>OCONHCCl$_3$; 8·38 broad s (1 H) NH. The coupling constant 6 Hz between the OCH and CHCOO protons was proved by double resonance. For $C_{14}H_{22}O_3$ (238·3) calculated: 70·56% C, 9·30% H; found: 70·70% C, 9·40% H. The ester *VII* (2·0 g) was equilibrated by heating with 0·3M methanolic sodium methoxide (50 ml) at 90°C for 14 hours. The usual isolation procedure followed by crystallisation from ligroin afforded 1·7 g (85%) of the ester *VIII* m.p. 102–104°C. NMR spectrum ($CDCl_3$, tetramethylsilane and trichloroacetyl isocyanate): 2·40 t (1 H) C<u>H</u>CO$_2$CH$_3$, $J_1 = 9·5$, $J_2 = 11·5$; 3·71 s (3 H) COCH$_3$; 5·12 t (1 H) C<u>H</u>O, $\Sigma J = 19$, $J_1 = J_2 = 9·5$. For $C_{14}H_{22}O_3$ (238·3) calculated: 70·56% C, 9·30% H; found: 70·84% C, 8·91% H.

TABLE III

First Order Rate Constants, k, for the Reaction of the Methanesulphonyl Derivatives *Id*–*IIId* and *Ie*–*IIIe* in the Presence of Potassium Acetate in Ethanol

For temperatures higher than 60°C the ampoule technique was used.

Compound	$10^5 k$, s^{-1} (temperature, °C)
Id	2·53 (80·0), 8·14 (90·0), 23·9 (100·0), 64·7 (110·0)
IId	6·60 (50·1), 21·5 (60·0), 63·6 (70·0)
IIId	1·62 (70·0)
Ie	0·539 (80·0), 2·09 (90·0), 7·33 (100·0), 23·1 (110·0)
IIe	6·49 (60·0), 20·8 (70·0), 58·5 (80·0)
IIIe	1·50 (70·0)

cis-4-Amino-*trans*-5-hydroxy-(*r*-3aH)-*trans*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene (*Ia*)

Treatment of the ester *VIII* (1·4 g) with hydrazine hydrate in ethanol (100°C, 4 hours) afforded 1·35 g of the hydrazide, m.p. 283—284°C (ethanol). For $C_{13}H_{22}N_2O_2$ (238·3) calculated: 11·75% N, found: 11·89% N. The hydrazide (1·30 g) was mixed with 0·93M-HCl (12·0 ml) and water was added till the solution became clear (200 ml). A solution of sodium nitrite (0·5 g) in water (15 ml) was then added under stirring and the mixture was stirred for 15 minutes. After the usual work-up procedure the crude azide was decomposed by boiling in ethanol (150 ml) for 1 hour. Evaporation of the solvent afforded 1·0 g of the crude urethane which was hydrolysed by refluxing with potassium hydroxide (5·5 g) in aqueous ethanol for 8 hours. The mixture was acidified with very dilute hydrochloric acid, extracted twice with ether, the product liberated from the aqueous layer by sodium hydroxide solution and taken into large amount of ether (about 1 liter) containing 10% of ethanol. Evaporation of the solvents afforded 0·6 g of *Ia*, m.p, 202—203°C (methanol). IR spectrum (C_2Cl_4, $5 . 10^{-3}$M) cm^{-1}: 3633, 3602 (sh), 3527 (OH). 3392, 3322 (NH). For $C_{12}H_{21}NO$ (195·3) calculated: 73·80% C, 10·84% H, 7·17% N; found: 73·99% C, 10·90% H, 7·40% N.

Inversion of *cis*-4-Benzamido-*trans*-5-methanesulphonyloxy-(*r*-3aH)-*trans*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene-(*Id*)

A solution of *Id* (502 mg, 1·33 mmol) and fused potassium acetate (167 mg, 1·7 mmol) in ethanol (40 ml) was heated in an autoclave to 120°C for 7 hours. The potassium methanesulphonate was filtered off and washed with ethanol, the filtrate was taken to dryness, shaken between aqueous sodium hydroxide solution and ether (4 x), the ethereal layer washed with water, dried and taken down. The residue (373·1 mg, 99·7%), m.p. 81—83°C, showed a single spot on thin-layer chromatography. It was dissolved in ether and treated with an ethereal solution of picric acid (320 mg, 1·4 mmol). The separated picrate, m.p. 177—178°C, weighed 627·3 mg (92·3%). For $C_{25}H_{26}N_4O_8$ (510·5) calculated: 58·82% C, 5·13% H, 10·97% N; found: 58·78% C, 5·18% H, 10·78% N. The oxazoline *XII*, m.p. 82·5—84·5°C, was liberated using lithium hydroxide solution, IR spectrum (KBr): 1625 cm^{-1} (C=N). For $C_{19}H_{23}NO$ (281·4) calculated: 81·10% C, 8·24% H, 4·98% N; found: 80·96% C, 8·54% H, 4·96% N.

cis-4-Amino-*cis*-5-hydroxy-(*r*-3aH)-*trans*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene (*IIIa*)

A suspension of the picrate of *XII* from the preceding preparation (592·1 mg) in water (150 ml) was heated under reflux for 3 hours. The picrate which separated on cooling melted then at 239—240°C (dec.). The whole reaction mixture was decomposed with sodium hydroxide (7 g) and boiled for 10 minutes. After cooling, the crystals were filtered off, washed with water, the filtrate extracted with ether and the ethereal layer taken down. The residue was combined with the crystals, dissolved in hot ethanol (10 ml), treated with a saturated aqueous solution of sodium hydroxide (100 mg) and boiled for 5 minutes. The mixture was diluted with water, the separated benzamide *IIIb* filtered off, washed with water and dried, yield 298·3 mg (86%), m.p. 208—209°C (ethanol). For analytical data see Table II. Boiling of *IIIb* (174·6 mg) with concentrated hydrochloric acid (35 ml) and ethanol (15 ml) for 50 hours afforded 77·7 mg (68%) of *IIIa*, m.p. 143 to 144°C, IR spectrum (C_2Cl_4, $5 . 10^{-3}$M), cm^{-1}: 3637, 3618 (weak), 3492 (OH), 3395 (NH). For $C_{12}H_{21}NO$ (195·3) calculated: 73·80% C, 10·84% H, 7·17% N; found: 73·90% C, 11·03% H, 7·13 %N.

Cyclisation of *IId*

A solution of *IId* (447·5 mg) and of fused potassium acetate (135 mg) in ethanol (30 ml) was heated in a glass ampoule to 100°C for two hours. The isolation procedure was the same as described for *Id*, and afforded 333·1 mg (99·9%) of product. Thin layer chromatography showed one major spot accompanied by another minor one. Chromatography on a silica gel column (70 g) with pentane–ether (3 : 2) as eluant afforded 307·5 mg (92%) of *XVII*, m.p. 90—92°C. IR spectrum (CCl_4), cm^{-1}: 1640 (strong) (C=N), 1496, 1581, 1603 (benzene ring); mass spectrum: M^+ 281, M 77, *m/e* 77, 105; high resolution: $C_{19}H_{23}NO$. NMR spectrum ($CDCl_3$, tetramethylsilane): 0·80—2·70 complex m (16 H), 4·30 d of doublets (1 H) CH—N, $J_{3a,4} = 4·5$ Hz, $J_{4,5} = 7·5$ Hz, 4·58 t (1 H) CH—O, $J_{4,5} = 7·5$ Hz, $J_{5,5a} = 8·0$ Hz, 7·30—7·55 m (3 H) *m*-and *p*-arom. H, 7·85—8·15 m (2 H) *o*-arom. H. For $C_{19}H_{23}NO$ (281·4) calculated: 81·10% C, 8·24% H, 4·98% N; found: 81·18% C, 8·32% H, 4·74% N. Further elution gave 15·4 mg of crystals, melting at 149 to 153°C. IR spectrum (CCl_4) cm^{-1}: 1672 (C—O), 3453 (N—H), 1632 (C—C), 1506, 1580, 1603 (benzene ring). Mass spectrum: M^+ 281, M-77, *m/e* 77,105.

trans-4-Amino-*trans*-5-hydroxy-(*r*-3aH)-*trans*-8a-*transoid*-8a,8b-*trans*-8b-perhydro-*as*-indacene (*XVIII*)

A solution of *XVII* (179 mg) in concentrated hydrochloric acid (25 ml) was refluxed for 50 hours. The mixture was diluted with water, extracted with ether and the aqueous layer was made alkaline with a sodium hydroxide solution. The liberated product was taken up into ether, the solution dried and taken down, leaving 108 mg (87%) of *XVIII*, m.p. 102—102·5°C. IR spectrum (C_2Cl_4, $5 . 10^{-3}$M) cm^{-1}: 3630 (free OH), 3483 (bonded OH). For $C_{12}H_{21}NO$ (195·3) calculated: 73·80% C, 10·84% H, 7·17% N; found: 73·53% C, 10·87% H, 7·08% N.

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