STEREOCHEMICAL STUDIES. LXXII.*

4,5-DISUBSTITUTED TWISTANES: VICINAL INTERACTIONS OH/CH_3 AND OH/CO_2CH_3 IN COMPOUNDS WITH THE TORSION ANGLE $\Theta \sim 30°$

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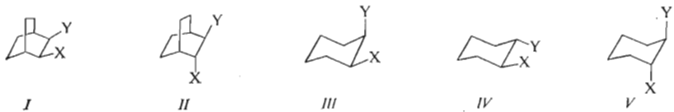
Diastereoisomeric vicinally 4,5-disubstituted derivatives of twistane (tricyclo[4,4,0,$0^{3,8}$]decane) have been prepared starting from 4-twistanone, and configurarion has been assigned to them on the basis of chemical relationships and NMR spectroscopy. Energy differences between epimers have been determined by chemical equilibration. From these energy differences the values of vicinal interactions OH/CH_3 and OH/CO_2CH_3 in compounds with the dihedral angle $\sim 30°$ have been estimated. For comparison, the values of vicinal interactions OH/CO_2CH_3 in epimeric methyl 5-tert-butyl-2-hydroxycyclohexanecarboxylates have been determined.

It is a well known phenomenon that the energetic content (or the magnitude of the interaction between substituents) in vicinally disubstituted molecules depends *inter alia* on the dihedral angle between the two vicinal substituents[1-3]. It is therefore of fundamental importance to know, at least semiquantitatively, the dependence of this interaction – attractive or repulsive – on the dihedral angle between substituents. Such knowledge is usually conditioned by the availability of suitable model systems with "guaranteed" fixed dihedral angles[4]. Thus, the angles $0-10°$ and $120 \pm \pm 10°$ may be found in the *cis*- and *trans*-2,3-disubstituted bicyclo[2,2,2]octane derivatives *I* and *II* respectively. Other, yet more flexible, models can be some biased or fixed compounds with cyclohexane ring, in which, assuming a homogeneous chair conformation, the axial-equatorial (*cis*), diequatorial and diaxial arrangement



I *II* *III* *IV* *V*

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may represent very approximately the values of $\Theta \leqq 60°$, $0 \geqq 60°$ and $\Theta \leqq 180°$, respectively (*III* – *V*). However, no suitable models have been known as yet which possess intermediate values, such as $\sim 30°$, $\sim 90°$ and $\sim 150°$.

One completely fixed system bearing such angles is the tricyclo[4,4,0,$0^{3,8}$]decane (twistane) system[5] where the torsional angles between bonds on $C_{(4)}$ and $C_{(5)}$ are 30°, 90° and 150° (Fig. 1). We therefore set out to synthesize some derivatives of twistane substituted at $C_{(4)}$ and $C_{(5)}$ and to study the energetic situation in them. In our previous papers[3,6,7] we determined the magnitude of vicinal interactions in systems *I* – *V* between suitable substituents. We applied now the same methods to the study of twistane derivatives.*

Synthesis and Assignment of Configuration

Reduction of 4-twistanone** (*VI*) with lithium aluminium hydride gave a mixture of *endo*- and *exo*-4-hydroxytricyclo[4,4,0,$0^{3,8}$]decanes (*VII* and *VIII*) in a ratio 1 : 5, from which the latter (*VIII*) was obtained by chromatography. The *endo*-isomer *VII* was obtained by equilibration of the reduction mixture with aluminium 2-propoxide followed by chromatographic separation of the alcohols (Scheme 1).

The alcohols were assigned configuration on the basis of the following reasoning: The study of models shows that the *exo*-isomer *VIII* contains more unfavourable interactions (the $OH/H_{(7)}$ interaction being probably decisive) than the *endo*-epimer *VII* and therefore it should be less populated under equilibration conditions. On the other hand, in the reduction of 4-twistanone the hydride anion should approach the carbonyl group from the less hindered side and therefore in the reduction mixture the *exo*-isomer *VIII* should predominate.

Consistent with this assignment is also the fact that lithium aluminium hydride reduction of the epoxide *IX* affords as a sole product the alcohol *VIII*. Since ammonolysis of the epoxide gives *trans*- amino alcohol with *exo*-4-configuration of the OH group[4,10] and both reactions are nucleophilic substitutions, we may anticipate an identical steric course, and consequently the configuration of the hydroxyl on $C_{(4)}$ in *VIII* should be *exo*. An unequivocal proof was given by the NMR spectra. The

**Note on nomenclature*: No obligatory universal stereochemical notation describing unequivocally stereoisomeric tricyclo[4,4,0,$0^{3,8}$]decane derivatives is available at present. In this paper we therefore describe the configuration of a given substituent in relation to the carbon $C_{(1)}$ of the system as the reference point[8]. The molecule is divided by a plane passing through the $C_{(4)}$—$C_{(5)}$ bond and through the centre of the $C_{(9)}$—$C_{(10)}$ bond, as depicted in Fig. 1. Now, if a substituent is on the same side of this plane as is the $C_{(1)}$ carbon, it has *endo*-configuration, if it is on the other side, its position is *exo*. It is evident that an unequivocal description is achieved only in connection with an appropriate numbering of the substituents: *exo*-4 position is equivalent to *endo*-5 position and *vice versa*.

** This compound was prepared according to Deslongchamps and coworkers[9]. These authors claim its m.p. to be 185—190°C. In our hands, however, the ketone melted at 173—174°C, as did the authentic specimen kindly sent by the Canadian authors to whom we thank.

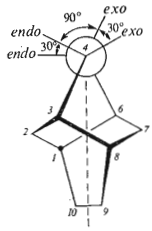
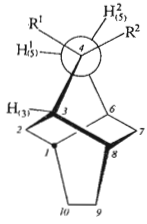


FIG. 1

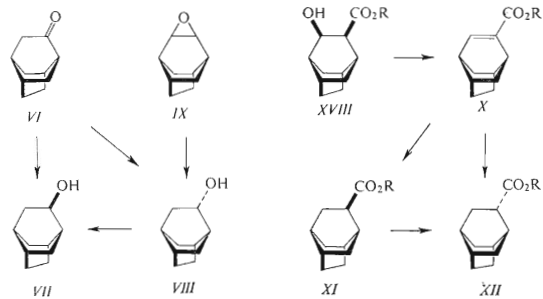
Torsion Angles between Bonds at $C_{(4)}$ and $C_{(5)}$



endo: $R^1 = OH$, $R^2 = H$
exo: $R^1 = H$, $R^2 = OH$

FIG. 2

Interactions between Carbinol Proton on $C_{(4)}$ and Protons on $C_{(3)}$ and $C_{(5)}$



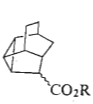
a; R = H
b; R = CH_3

SCHEME 1

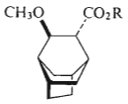
carbinol proton of the *endo*-epimer *VII* exhibits a triplet with two interaction constants $J \sim 7{\cdot}2$ Hz whereas the spectrum of the isomer *VIII* has a quartet with $J \sim 7{\cdot}5$ Hz and 4·2 Hz. As seen on models, the carbinol proton in both isomers interacts with three vicinal protons, $H_{(3)}$, $H^1_{(5)}$ and $H^2_{(5)}$ (Fig. 2). In the *endo*-isomer *VII* the torsion angle $H_{(4)}—C_{(4)}—C_{(3)}—H_{(3)}$ is $\sim 75°$, $H_{(4)}—C_{(4)}—C_{(5)}—H^1_{(5)} \sim 150°$ and $H_{(4)}—C_{(4)}—C_{(5)}—H^2_{(5)} \sim 30°$ which, according to the Karplus relation[11,12], corresponds to one very small and two great interactions of nearly the same magnitude

(triplet). In the *exo*-isomer *VIII* the respective torsion angles are about 45°, 30° and 90°, corresponding thus to one small, one greater and one negligible interaction (quartet).

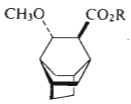
The two monocarboxylic acids *XI* and *XII* were obtained by catalytic reduction (Scheme 1) of the unsaturated acid *Xa* as a 4 : 1 mixture. One epimer (*XI*) was isolated by crystallisation from pentane (−70°C), the other (*XII*) was obtained by equilibration of the esters and subsequent hydrolysis followed by crystallisation of the mixture of acids (*XI* : *XII* ~ 3 : 7). Configuration was assigned to the acids on the basis of their stability and of coupling constants of the α-proton in NMR spectra, analogously as in the case of the alcohols.



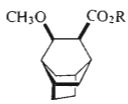
XIII



XIV



XV



XVI

a; R = H
b; R = CH_3

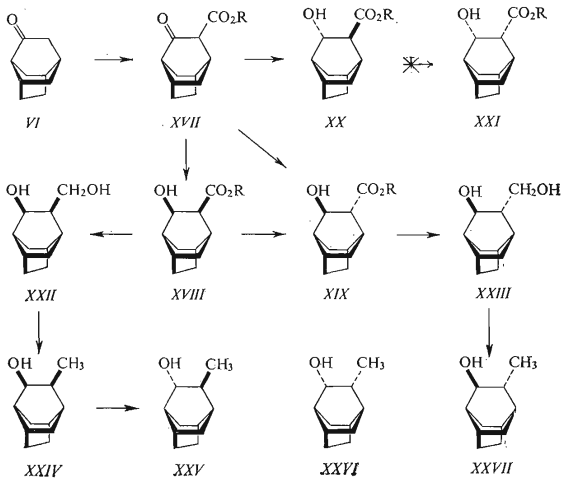
The required unsaturated acid *Xa* was prepared by dehydration of the *cis*-hydroxy ester *XVIIIb* followed by saponification. When this elimination was carried out using $POCl_3$ in pyridine, two compounds were obtained in a 3 : 2 ratio which were separated by preparative vapour phase chromatography, the minor compound being the unsaturated ester *Xb* according to NMR, IR and UV spectra and analysis. The other compound had the same analysis and molecular weight but did not contain double bond. This compound might have the structure *XIIIb* which would arise from a non-classical ion, similarly as the tricyclane system arises from a bicyclo[2,2,1]heptane derivative[13,14]. Superior method of preparing the unsaturated ester *Xb* was found in the dehydration of *XVIIIb* by heating in hexamethylphosphortriamide to 240°C (ref.[15]); this reaction gives exclusively pure *Xb*. To eliminate the possibility that *Xb* is also a rearrangement product we proved its twistane skeleton on a chemical way. Treatment of *Xb* with sodium methoxide in methanol afforded two methoxy esters in a ratio 1 : 4. These were transformed into a mixture of methoxy acids from which an acid was isolated, which was identical with the methoxy acid *XIVa* prepared from the hydroxy ester *XIXb* by treatment with methyl iodide.

The formation of the methoxy esters deserves comment. These compounds arise not only by the action of sodium methoxide on the unsaturated ester but also on the hydroxy esters themselves. The formation of methoxy esters was observed in all cases of equilibration of vicinal hydroxy esters of cyclohexane as well as twistane series. We suppose that in the twistane series

these methoxy derivatives are formed *via* the unsaturated ester *Xb*, because the action of 2M sodium methoxide in methanol on the *cis*-hydroxy ester *XVIIIb* and on the unsaturated ester *Xb* results in an identical mixture of two methoxy esters, the main product being *XIVb* and the other having the same retention time as the *cis*-methoxy ester *XVIb*.

A similar case was observed already by Ingold[16] who found that β-hydroxy esters react with ethyl cyanoacetate in such a way as if the esters were dehydrated and then subjected to Michael addition. In our case the addition of methanol on the unsaturated ester *Xb* is apparently kinetically controlled since the product is not *XVb* which should be the thermodynamically most stable isomer, but only the less stable ester *XIVb* together with *XVIb*.

Carboxylation of 4-twistanone (*VI*) followed by catalytic reduction of the resulting keto acid *XVIIa* over platinum in acetic acid gave as the main product the hydroxy acid *XVIIIa*, m.p. 166–167·5°C (Scheme 2). This, on isomerisation *via* the ester *XVIIIb*, gave predominantly another acid *XIXa*, m.p. 188–190°C. Sodium borohydride reduction of *XVIIa* afforded a mixture of the above-mentioned acids, together with a third isomer *XXa*, m.p. 184–186°C, (*XVIIIa* : *XIXa* : *XXa* = 5 : 2·5 : 1) which was isolated by very careful chromatographic separation of the esters on silica gel and by subsequent saponification.

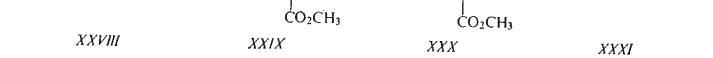


a; R = H
b; R = CH_3

SCHEME 2

The esters *XVIIIb*, *XIXb* and *XXb* were assigned the configuration shown in Scheme 2 on the basis of the following facts: The IR-spectrum of the ester *XIXb* prepared by isomerisation of *XVIIIb* exhibits only a free hydroxyl band, whereas the spectrum of *XVIIIb* shows the presence of a strong intramolecular hydrogen bond ($\Delta\nu = 95$ cm^{-1}) and the third isomer *XXb* is only weakly hydrogen-bonded ($\Delta\nu = 15$ cm^{-1}). A proof of this assignment was given by the signals of the carbinol proton in the NMR spectrum of the esters. The ester *XVIIIb* exhibits a quartet with interaction constants 6·5 Hz and 4·8 Hz, the ester *XIXb* shows a doublet with $J = 7{\cdot}0$ Hz and the ester *XXb* also a doublet with $J = 4{\cdot}4$ Hz. As shown by models, the spectrum of *XVIIIb* indicates the *cis*-relationship of the functional groups (*exo*-4-OH-*exo*-5--CO_2CH_3) where the torsion angle $H_{(4)}—C_{(4)}—C_{(5)}—H_{(5)}$ is $\Theta_1 \sim 30°$ and $H_{(4)}—C_{(4)}—C_{(3)}—H_{(3)}$ is $\Theta_2 \sim 45°$. The doublet exhibited by *XIXb* is consistent with $\Theta_1 \sim 90°$ and $\Theta_2 \sim 45°$, respectively, and therefore the torsion angle HO—C—C—CO_2CH_3 is 150°. The J value of the isomer *XXb* confirms the respective angles $\Theta_1 \sim 150°$ and $\Theta_2 \sim 75°$ and thus 90° for the HO—C—C—CO_2CH_3 angle. The assignment of configuration to the hydroxy acids was further supported by chemical transformations of the corresponding amino alcohols[4,10].

Only three diastereoisomers of 4-hydroxy-5-methyltricyclo[4,4,0,$0^{3,8}$]decane (*XXIV*, *XXV* and *XXVII*) were prepared. Two of them were synthesized from the corresponding hydroxy esters *XVIIIb* and *XIXb* *via* the diols *XXII* and *XXIII*. Treatment of these diols with methanesulphonyl chloride in pyridine at −50°C followed by reduction of the resulting primary monomethanesulphonates[17] with lithium aluminium hydride afforded *XXIV* and *XXVII*. The third isomer, *XXV*, was obtained by equilibration of the alcohol *XXIV* with aluminium 2-propoxide in 2-propanol. The fourth isomer, *XXVI*, was not isolated and was detected as the only one new peak in the vapour phase chromatogram of the equilibrium mixture arising from *XXIV*.



XXVIII *XXIX* *XXX* *XXXI*

Vicinal Interactions in Disubstituted Twistanes

Before assessing the vicinal interactions in the disubstituted derivatives, it was necessary to know the energy difference ΔG between the *exo* and *endo* position in monosubstituted derivatives. We therefore equilibrated 4-hydroxy- and 4-methoxycarbonyl derivatives *VII*, *VIII*, *XI* and *XII*. In both cases the *endo*-4-isomer is the more stable one, the equilibrium constant being at 90°C $K_{OH} = 1{\cdot}69$ and $K_{CO_2CH_3} = 3{\cdot}18$, which

corresponds to ΔG 0·38 kcal mol^{-1} and 0·84 kcal mol^{-1}, respectively (Table I). These values are lower than the corresponding energy difference between equatorial and axial position of hydroxy and methoxycarbonyl group in the chair form of cyclohexane. This is interesting because one would expect a relatively great energy difference between the *endo*- and the *exo*-isomer caused by the severe 1,4-interaction between hydrogen on $C_{(7)}$ and the substituent in the *exo*-4-isomer.

The comparison of the vicinal interaction in twistane derivatives having $\Theta \sim 30°$ with systems with $\Theta \sim 0°$ and 60° may afford a semiquantitative illustration of the change of the magnitude of the vicinal interaction between given substituents in relation to the torsion angle. As suitable groups we considered methyl and hydroxyl for the following reasons: Methyl is a symmetrical rotor and therefore it has no energetically different rotamers. Further, the vicinal OH/CH_3 interactions were already determined by us[3,6] for systems with $\Theta \sim 0°$ and $\Theta \sim 60°$.

Under the plausible assumption that in the *trans*-isomer *XXV* there is no appreciable interaction between hydroxyl and methyl group ($\Theta \sim 90°$), we may write for the equilibrium *XXV* ⇄ *XXIV* the equation

$$\Delta G_{vic} = \Delta G_{OH} - \Delta G_{exp}\,, \qquad (I)$$

where ΔG_{vic} is the net vicinal interaction, ΔG_{OH} is the energy difference between *endo*- and *exo*-hydroxyl and ΔG_{exp} is the energy difference found for the epimerisation *XXV* ⇄ *XXIV* (Table I). Taking 0·43 kcal mol^{-1} for $-\Delta G_{OH}$ at 160°C and 2·33 kcal mol^{-1} for ΔG_{exp} we obtain $\Delta G_{vic} = 2{\cdot}33 - 0{\cdot}43 = 1{\cdot}90$ kcal mol^{-1}. Similarly, for the equilibrium *XXVII* ⇄ *XXVI* (Table I) the $\Delta G_{vic} = 0{\cdot}43 + 1{\cdot}67 = 2{\cdot}10$

TABLE I
Equilibrium Compositions and the Corresponding ΔG Values

Equilibrium	°C/h	% (Isomer)[a]	ΔG, kcal/mol
VII ⇄ *VIII*	90/140[b]	36·9 (*VIII*)	0·39
	160/100[b]	37·8 (*VIII*)	0·43
XIb ⇄ *XIIb*	90/60[c]	23·8 (*XIb*)	−0·84
XXIV ⇄ *XXV*	160/120[b]	6·2 (*XXIV*)	−2·33
XXVI ⇄ *XXVII*[d]	160/90[b]	12·5 (*XXVI*)	
	160/120[b]	12·5 (*XXVI*)	−1·67
XVIIIb ⇄ *XIXb*	40/14[c]	21·0 (*XVIIIb*)	−0·82
XXVIII ⇄ *XXX*	40/52[c]	2·1 (*XXX*)	2·39
XXIX ⇄ *XXXI*	40/52[c]	16·7 (*XXIX*)	−1·00

[a] Results of at least two independent equilibrations starting from both epimers; [b] in 0·2M aluminium 2-propoxide; [c] in 0·2M sodium methoxide; [d] only from the side of *XXVII*.

kcal mol^{-1}. It is evident that, although in these two experiments the steric environment of the substituents is reversed, the value of the vicinal interaction is nearly the same. This indicates that the magnitude of the vicinal interaction OH/CH_3 in this system does not depend significantly on the steric enviroment of the groups. The values of vicinal OH/CH_3 interactions, ΔG_{vic}, for various torsion angles are thus as follows.*

Θ	0—10°	~30°	~60°
ΔG_{vic} kcal mol^{-1}	3·6[a]	2·0[b]	0·4[c]

Having in hand the three isomeric hydroxy esters *XVIIIb*—*XXb* we determined the vicinal interactions also in these compounds. Here, however, the determination of OH/CO_2CH_3 is complicated by several factors. First, whereas methyl is a symmetrical group, the methoxycarbonyl group is highly unsymmetrical and therefore its interaction with the neighbouring hydroxyl may seriously be affected by its environment[18,19], *i.e.* the change of its optimum conformation going from a monosubstituted to a disubstituted vicinal derivative may be different in different systems. Therefore, the value of interaction found in the present case is likely to be valid only for the twistane hydroxy esters.

Analogously to the equation (*1*), we may write for the OH/CO_2CH_3 interaction in the twistane derivatives $\Delta G_{vic} = -\Delta G_{CO_2CH_3} - \Delta G_{exp} = 0{\cdot}84 + 0{\cdot}82 = 1{\cdot}66$ kcal mol^{-1}, where $\Delta G_{CO_2CH_3}$ is the energy difference between *endo*- and *exo*-metoxycarbonyl group and ΔG_{exp} is the experimentally found energy difference between the *cis*-isomer *XVIIIb* and the *trans*-isomer *XIXb* (Table I).**

Of the second pair of isomers only the *endo*-4-hydroxy-*exo*-5-methoxycarbonyl derivative *XX* was available. Attempts to equilibrate this ester to obtain the second *cis*-ester *XXIb* evidently failed as shown by vapour phase chromatographic analysis on many columns which revealed no new peak in the hydroxy ester region. Instead, on longer reaction time, higher temperature or higher concentration of sodium methoxide, another two peaks of low retention time were observed which were shown to be the isomeric 4-methoxy-5-methoxycarbonyltricyclo[4,4,0,0^{3,8}]decanes. If we suppose as a first approximation that the vicinal interaction in the unknown *cis*-isomer *XXIb* is the same as in *XVIIIb*, we may estimate that for the equilibrium *XXb* $\rightleftarrows$ *XXIb* $\Delta G_{exp} = \Delta G_{CO_2CH_3} + \Delta G_{vic} = 0{\cdot}83 + 1{\cdot}65 = 2{\cdot}48$ kcal mol^{-1}, *i.e.* the equilibrium mixture should contain at 40°C only about 1·8% of the *cis*-isomer *XXI*.

* [a] Determined on bicyclo[2,2,2]octane derivatives[3]; [b] mean value; [c] value for *trans*-4-tert-butyl-*trans*-2-methylcyclohexanol[6].

** $\Delta G_{CO_2CH_3}$ was determined at 90°C, whereas the ΔG_{exp} at 40°C. We feel that the energy values are comparable because the ΔG value will not change dramatically to affect the calculated value of ΔG_{vic}; *e.g.* in twistane system the ΔG_{OH} values at 90°C and 160° differ only for about 0·04 kcal mol^{-1}.

Nevertheless, the fact that even this small amount was not observed may be explained by a greater rate of formation of the methoxy esters from the *cis*-isomer *XXI* than its rate of formation from the *trans*-isomer *XX*.

For illustration we performed the equilibration of the biased cyclohexane hydroxy esters *XXVIII*–*XXXI* which were hitherto not studied. The four stereoisomeric methyl 2-hydroxy-5-tert-butylcyclohexanecarboxylates[22] *XXVIII*–*XXXI* were equilibrated under the same conditions as the twistane derivatives. The results of equilibration are listed in Table I. The corresponding repulsive vicinal OH/CO_2CH_3 interactions, ΔG_{vic}, were calculated in the same way as described elsewhere[6,7] and are listed below.

Compound	*XVIIIb*	*XXX*	*XXXI*	*XXVIII*
ΔG_{vic} kcal mol^{-1}	1·7	≧1·0*	0·4	0*

As evident, only pairs *XXVIII* ⇄ *XXX* and *XXIX* ⇄ *XXXI* were equilibrated and therefore the calculated interaction in *XXX* depends on the magnitude of the interaction between the equatorial groups in *XXVIII*; this was tentatively taken as zero. This is certainly not far from the actual value because analogous interaction between equatorial methyl and equatorial methoxycarbonyl group is very small[7] (0·2 kcal mol^{-1}) and substitution of methyl for the smaller hydroxy group will likely reduce the interaction.

EXPERIMENTAL

The isomeric methyl 2-hydroxy-5-tert-butylcyclohexanecarboxylates *XXVIII*, *XXX* and *XXXI* are known[22]; the isomer *XXIX* was prepared *in situ* from the known acid[23] by treatment with diazomethane.

exo-4-Hydroxy(*r*-1)tricyclo[4,4,0,0^{3,8}]decane (*VIII*)

A) Lithium aluminium hydride reduction (810 mg, 30 ml, ether) of 4-twistanone[9] (*VI*) (3·0 g in 30 ml of ether) afforded after the usual work-up procedure 2·97 g of a 83: 17 mixture of *VIII* and *VII* which was chromatographed on a silica gel column (1 000 g). Elution with ether–light petroleum (1 : 4) afforded 1·95 g (65%) of pure *VIII* which after crystallisation from ligroin melted at 202–203°C (sealed capillary). IR spectrum (10^{-3}M, CCl_4): 3 626 cm^{-1}; NMR spectrum ($CDCl_3$): 0·9–2·1 m (14 H), 4·02 q, $J_1 \sim 7{\cdot}5$ Hz, $J_2 \sim 4{\cdot}2$ Hz (1 H, carbinol proton on $C_{(4)}$). For $C_{10}H_{16}O$ (152·2) calculated: 78·89% C, 10·59% H; found: 78·92% C, 10·46% H.

B) A solution of lithium aluminium hydride (10 mg; 0·26 mmol) and aluminium chloride (7 mg; 0·06 mmol) in ether (0·5 ml) was added to a stirred solution of *IX* (50 mg) in ether (0·5ml). The reaction mixture was stirred at room temperature for 20 min, decomposed with water, dried, evaporated and the residue sublimed giving 30 mg (60%) of the alcohol *VIII*, m.p. 198–200°C, undepressed on admixture of an authentic sample prepared by route *A*).

* From the equilibration *XXX* ⇄ *XXVIII* assuming the $\Delta G_{vic} = 0$ in *XXVIII*.

endo-4-Hydroxy(*r*-1)-tricyclo[4,4,0,0^{3,8}]decane (*VII*)

The ketone[9] *VI* (3·0 g) was reduced as described in the preceding experiment. The mixture of epimers was dissolved in 40 ml of 1M aluminium 2-propoxide in 2-propanol and heated to 120°C for 50 h. The reaction mixture was diluted with 1M-HCl (350 ml) and extracted with ether (6× 30 ml), the combined etheral layers were washed with water, dried and taken down. The residue (2·95 g) which contained 64% of *VII* was chromatographed on a silica gel column (450 g) affording on elution with ether–light petroleum (1 : 5) 1·2 g (40%) of pure *VII*, m.p. 142—143°C (light petroleum). IR-spectrum (10^{-3}M, CCl_4): 3 622 cm^{-1} NMR spectrum ($CDCl_3$): 1·1—2·2 m (14 H), 4·16 t, $J_1 = J_2$ 7·2 Hz (1 H, carbinol proton on $C_{(4)}$). For $C_{10}H_{16}O$ (152·2) calculated: 78·89% C, 10·59% H; found: 79·10% C, 10·44% H.

4,5-Epoxytricyclo[4,4,0,0^{3,8}]decane (*IX*)

A solution of *p*-nitroperoxybenzoic acid (1·6 g, 8·75 mmol) in ether (25 ml) was added to a solution of 4-tricyclo[4,4,0,0^{3,8}]decene[20] (485 mg, 3·62 mmol) in ether (5 ml) and the mixture was set aside for 48 h at room temperature, then shaken with 10% aqueous NaOH (50 ml) and water (2 × 30 ml), dried and evaporated through a small column. Chromatography of the residue on silica gel (50 g, ether–light petroleum 1 : 4) followed by sublimation afforded 380 mg (70%) of the epoxide *IX*, m.p. 188—190°C (sealed capillary). For $C_{10}H_{14}O$ (150·2) calculated: 79·96% C, 9·39% H; found: 79·86% C, 9·43% H.

4-Methoxycarbonyltricyclo[4,4,0,0^{3,8}]dec-4-ene (*Xb*)

A) A solution of *XVIIIb* (500 mg) in hexamethylphosphortriamide (1·5 ml) was heated to 220—230°C for 30 min, the cooled mixture was diluted with water (10 ml) and the product taken into pentane (3 × 2 ml), washed with water, dried and taken down. The residue was purified by chromatography on silica gel (10 g, ether–pentane 1 : 2) followed by distillation at 130 to 140°C/12 Torr (bath temperature) giving 210 mg (46%) of *Xb*. For $C_{12}H_{16}O_2$ (192·2) calculated: 74·97% C, 8·39% H; found: 74·81% C, 8·28% H. IR-spectrum (CCl_4): 1 618 cm^{-1} (conjug. CO_2CH_3); UV-spectrum (6·5 . $10^{-3}M$, ethanol): λ_{max} 232 nm (log ε 3·86); NMR spectrum ($CDCl_3$): 0·9—2·0 m (10 H), 2·81 q (1 H, proton on $C_{(6)}$), 3·24 t (1 H, proton on $C_{(3)}$), 3·74 s (3 H, CH_3), 7·385 q, $J_1 \sim 7$ Hz, $J_2 \sim 2$ Hz (1 H, olefinic proton on $C_{(5)}$); *m/e* 192.

B) A solution of phosphorus oxychloride (1·5 ml; 2·55 g; 16·4 mmol) in pyridine (7·6 ml) was added to a solution of *XVIIIb* (2·3 g, 10·95 mmol) in pyridine (4·6 ml). The mixture was refluxed for 20 min, cooled, diluted with water (100 ml), extracted with pentane (4 × 20 ml), the combined organic layers washed with water, dried and the solvent evaporated. Distillation of the residue gave 1·5 g (71·5%) of a fraction, b.p. 145—160°C/15 Torr consisting, according to vapour phase chromatography on poly(ethylene glycol adipate), of two compounds *XIIIb* and *Xb* (3 : 2) which were separated by vapour phase chromatography. The compound *XIIIb* has molecular weight 192 (mass spectroscopy), IR-spectrum (CCl_4): 1 738 cm^{-1} (unconjugated CO_2CH_3); UV-spectrum: transparent in the 200—300 nm region., NMR-spectrum ($CDCl_3$): 0·8—2·2 m (12 H), 2·99 q (1 H, proton on $C_{(4)}$), 3·69 m (3 H, CH_3). For $C_{12}H_{16}O_2$ (192·2) calculated: 74·97% C, 8·39% H; found: 74·93% C, 8·44% H. The compound *Xb* was in every respect identical with the sample obtained ad *A*).

4-Tricyclo[4,4,0,0^{3,8}]dec-4-enecarboxylic Acid (*Xa*)

Saponification of *Xb* (310 mg) by boiling with a solution of KOH (130 mg) in 50% ethanol (1 ml) followed by the usual isolation procedure gave a compound which on crystallisation from 70% ethanol afforded 170 mg (60%) of the acid, m.p. 149—151°C. For $H_{11}H_{14}O_2$ (178·2) calculated: 74·13% C, 7·92% H; found: 73·97% C, 7·97% H. Molecular weight 178 (mass spectroscopy).

exo-4-(*r*-1)Tricyclo[4,4,0,$0^{3,8}$]decanecarboxylic Acid (*XIa*)

Hydrogenation of the acid *Xa* (115 mg, 0·65 mmol) in acetic acid (5 ml) over platinum oxide (55 mg) afforded two isomeric acids *XI* and *XII* in a ratio 4 : 1. Three crystallisations from pentane (−70°C) gave 30·5 mg (26%) of the pure *exo*-acid *XI*, m.p. 94−95°C. For $C_{11}H_{16}O_2$ (180·3) calculated: 73·30% C, 8·95% H; found: 73·41% C, 9·13% H. NMR-spectrum ($CDCl_3$): 1·1−2·35 m (14 H), 2·63 broad q, J_1 ~10 Hz, J_2 ~3·5 Hz (1 H, proton on $C_{(4)}$); *m/e* 180.

endo-4-(*r*-1)Tricyclo[4,4,0,$0^{3,8}$]decanecarboxylic Acid (*XIIa*)

The mixture of acids obtained by catalytic reduction of *Xa* (111 mg) was esterified with diazomethane and equilibrated by heating with 8 ml of 0·2M methanolic sodium methoxide in a sealed ampoule to 100°C for 30 h. The mixture was partially evaporated, refluxed with an aqueous solution (15 ml) of NaOH (250 mg) for 2 h, taken to dryness, dissolved in water (5 ml) and washed with ether. The aqueous layer was acidified with dil. (1 : 1) HCl, the product was taken into ether, dried and the ether was evaporated leaving 85 mg (77%) of a crystalline mixture of *XI* and *XII* (3 : 7). Two crystallisations from pentane (−70°C) afforded 21 mg (19%) of the *endo*-acid *XII*, m.p. 94−96°C. NMR-spectrum ($CDCl_3$): 1·1−2·3 m (14 H), 2·76 t, $J_1 = J_2$ ~8·5 Hz (1 H, proton on $C_{(4)}$); *m/e* 180.

4-Oxo-5-tricyclo[4,4,0,$0^{3,8}$]decanecarboxylic Acid (*XVIIa*)

4-Twistanone *VI* (9·3 g, 62 mmol) was carboxylated in ether (300 ml) with triphenylmethyl potassium prepared from 18·8 g (77 mmol) of triphenylmethane and 3 g (77 mmol) of potassium analogously to the procedure described elsewhere[21,22]. The usual isolation procedure afforded 9·4 g (78·5%) of the keto acid *XVIIa*, decomposing at 130−131°C (acetone–water).

Methyl ester (*XVIIb*) was obtained by treatment with diazomethane, m.p. 105−107°C (methanol). IR-spectrum (CCl_4): 1 745 cm^{-1} (C=O), 1 725, 1 438, 1 172 cm^{-1} (CO_2CH_3). For $C_{12}H_{16}O_3$ (208·2) calculated: 69·21% C, 7·74% H; found: 69·39% C, 7·75% H.

exo-4-Hydroxy-*exo*-5-(*r*-1)tricyclo[4,4,0,$0^{3,8}$]decanecarboxylic Acid (*XVIIIa*)

The keto acid *XVIIa* (5·7 g, 29·4 mmol) was hydrogenated in acetic acid (140 ml) over platinum oxide (2·0 g), the catalyst was filtered off and the solution evaporated to dryness and dried 20 h *in vacuo*. One crystallisation from ether followed by two from ethyl acetate gave 4·6 g (80%) of pure *cis*-acid (*XVIIIa*), m.p. 166−167·5°C. For $C_{11}H_{16}O_3$ (196·2) calculated: 67·32% C, 8·22% H; found: 67·53% C, 8·26% H.

exo-4-Hydroxy-*endo*-5-methoxycarbonyl(*r*-1)tricyclo[4,4,0,$0^{3,8}$]decane (*XIXb*) and *endo*-4-Hydroxy-*exo*-5-methoxycarbonyl(*r*-1)tricyclo[4,4,0,$0^{3,8}$]decane (*XXb*)

To a stirred slurry of *XVIIa* (9·7 g, 50 mmol) in water (40 ml) an aqueous solution (17 ml) of NaOH (2·065 g, 51·5 mmol) was added at 0°C, followed by 2·49 g (66 mmol) of sodium borohydride. The mixture was allowed to stand at room temperature for 5 h, diluted with water (150 ml), washed with ether (2 × 50 ml) and acidified with dilute (1 : 1) hydrochloric acid. The precipitate was taken up in ether (6 × 50 ml), washed with water, dried and taken down leaving 9·6 g of crystalline mixture of acids which upon treatment with diazomethane and distillation at 118−121°C/0·2 Torr gave 9·7 g of a mixture of esters *XVIIIb*, *XIXb* and *XXb* in the ratio 5 : 2·5 : 1. The esters were heated with 0·2M methanolic sodium methoxide (44 ml) to 50°C

for 3·5 h. The reaction mixture was taken between water (350 ml) and light petroleum (100 ml), the organic layer washed with water, dried and taken down. According to vapour phase chromatography, the residue (8·1 g, 91%) contains 12% of the isomeric 4-methoxy-5-methoxycarbonyltricyclo[4,4,0,0^{3,8}]decanes, 15% of *XVIIIb*, 50% of *XIXb* and 23% of *XXb*. Chromatography of this mixture (6·4 g) on a silica gel column (2·2 kg) using benzene with 8% ether as eluent afforded 4 principal fractions. The first fraction consisted of stereoisomeric methoxy esters (0·7 g). From the second fraction *XVIIIb* (1·1 g), m.p. 50—52°C (pentane), was obtained, identical with the ester obtained from the acid *XVIIIa* prepared by catalytic reduction of *XVIIa*. IR-spectrum (10^{-3}M, CCl_4): 3 520 cm^{-1} (bonded OH), 3 615 cm^{-1} (free OH); NMR-spectrum ($CDCl_3$): 1·1—2·2 m (12 H), 2·79 broad d, $J \sim 6{\cdot}5$ Hz (1 H, proton on $C_{(5)}$), 3·73 s (3 H, CH_3), 4·25 q $J_1 \sim 6{\cdot}5$ Hz, $J_2 \sim 4{\cdot}8$ Hz (1 H, proton on $C_{(4)}$). For $C_{12}H_{18}O_3$ (210·3) calculated: 68·54% C, 8·63% H; found: 68·83% C, 8·57% H. Third fraction contained *XIXb*, b.p. 120°C/0·2 Torr (2·3 g). IR-spectrum (4·7 . 10^{-3}M, CCl_4): 3 626 cm^{-1} (free OH); NMR spectrum ($CDCl_3$): 1·1—2·2 m (12 H), 2·02 broad d, $J \sim 4{\cdot}4$ Hz (1 H, proton on $C_{(5)}$), 3·69 s (3 H, CH_3), 4·45 broad d (1 H, proton on $C_{(4)}$. For $C_{12}H_{18}O_3$ (210·3) calculated: 68·54% C, 8·63% H; found: 68·65% C, 8·69% H. The last fraction (0·6 g) afforded *XXb*, m.p. 45·5—47°C (pentane). IR-spectrum (4·91 . . 10^{-3}M, CCl_4): 3 608 cm^{-1} (bonded OH), 3 624 cm^{-1} (free OH); NMR-spectrum ($CDCl_3$): 1·1—2·2 m (12 H), 2·53 broad d, $J \sim 7{\cdot}0$ Hz (1 H, proton on $C_{(5)}$), 3·72 s, (3 H, CH_3), 4·35 broad d, $J \sim 7{\cdot}0$ Hz (1 H, proton on $C_{(4)}$). For $C_{12}H_{18}O_3$ (210·3) calculated: 68·54% C, 8·63% H; found: 68·65%C, 8·46% H.

exo-4-Hydroxy-*endo*-5-(*r*-1)tricyclo[4,4,0,0^{3,8}]decanecarboxylic Acid (*XIXa*)

The corresponding ester *XIXb* (200 mg) was saponified by boiling with sodium hydroxide (250 mg) in 50% methanol (4 ml) for 4 h. The usual isolation procedure gave *XIXa* contaminated with about 27% of *XVIIIa*. Three crystallisations of this material from ethyl acetate afforded 70 mg (42%) of the pure *XIXa*, m.p. 188—190°C. For $C_{11}H_{16}O_3$ (196·2) calculated: 67·32% C, 8·22% H; found: 67·42% C, 8·33% H.

endo-4-Hydroxy-*exo*-5-(*r*-1)tricyclo[4,4,0,0^{3,8}]decanecarboxylic Acid (*XXa*)

Saponification of the ester *XXb* (500 mg, 2·4 mmol) with KOH (180 mg) in 50% aqueous ethanol (1·4 ml) at 90°C for 15 min afforded after the usual work-up procedure and two crystallisations from ethyl acetate 360 mg (77·5%) of the pure *XXa*, m.p. 184—186°C. For $C_{11}H_{16}O_3$ (196·2) calculated: 67·32% C, 8·22% H; found: 67·54% C, 8·32% H.

exo-4-Hydroxy-*exo*-5-methyl(*r*-1)tricyclo[4,4,0,0^{3,8}]decane (*XXIV*)

The hydroxy ester *XVIIIb* (100 mg) was reduced with lithium aluminium hydride (150 mg) in ether (7 ml). After 30 min the mixture was decomposed with water and 15% NaOH, the inorganic material filtered off and washed thoroughly with chloroform. The washings were combined with the original filtrate, dried and taken down, leaving 81 mg (93%) of *exo*-4-hydroxy-*exo*-5--hydroxymethyl(*r*-1)tricyclo[4,4,0,0^{3,8}]decane (*XXII*), m.p. 106—109°C (ether). For $C_{11}H_{18}O_2$ (182·3) calculated: 72·49% C, 9·96% H; found: 72·56% C, 9·93% H.

A solution of methanesulfonyl chloride (775 mg, 6·8 mmol) in pyridine (3 ml) was added to a stirred solution of *XXII* (1·2 g, 6·6 mmol) in pyridine (5 ml) at −50°C. The mixture was allowed to stand for 3 h at room temperature, diluted with water (100 ml), the product taken up into ether (4 × 15 ml), washed with 0·5M-HCl, water, and saturated hydrogen carbonate solution, dried, and taken down. The residue (1·8 g) was dissolved in ether (10 ml), added to a stirred ethereal

solution of lithium aluminium hydride (1·5 g in 30 ml) and set aside overnight. The product was isolated in the usual manner and purified by chromatography on silica gel (200 g, pentane–ether 2 : 1). The distillation at 145—170°C/15 Torr (bath temperature) gave 785 mg (72%) of *XXIV*, m.p. 49—50°C (in bulk). IR-spectrum ($4{\cdot}52 \cdot 10^{-3}$M, CCl_4): 3633 cm^{-1} (OH). For $C_{11}H_{18}O$ (166·3) calculated: 79·46% C, 10·92% H; found: 79·38% C, 10·83% H.

exo-4-Hydroxy-*endo*-5-methyl(*r*-1)tricyclo[4,4,0,$0^{3,8}$]decane (*XXVII*)

The ester *XIXb* was reduced in 83% yield to *exo*-4-hydroxy-*endo*-5-hydroxymethyl(*r*-1)tricyclo-[4,4,0,$0^{3,8}$]decane (*XXIII*), m.p. 111—114°C (ether), as described in the preceding experiment. For $C_{11}H_{18}O_2$ (182·3) calculated: 72·49% C, 9·96% H; found: 72·49% C, 9·48% H. The diol *XXIII* was converted, again as described above, *via* methanesulphonate into *XXVII*, m.p. 81 to 82·5°C (pentane) in 41% yield. For $C_{11}H_{18}O$ (166·3) calculated: 79·46% C, 10·92% H; found: 79·69% C, 11·11% H.

endo-4-Hydroxy-*exo*-5-methyl(*r*-1)tricyclo(4,4,0,$0^{3,8}$)decane (*XXV*)

A solution of *XXIV* (735 mg) and aluminium 2-propoxide (1·5 g) in 2-propanol (10·5 ml) was heated in a sealed ampoule to 140°C for 120 h. The mixture was then diluted with 1M-HCl (100 ml), the product was taken up into ether (6 × 15 ml), washed with water, dried and the solvent distilled off using a column. The residue which contained 90% of *XXV* and 10% of *XXIV*, was subjected to chromatography on silica gel (250 g, ether–light petroleum 1 : 2) yielding 50 mg of the starting *XXIV*, 210 mg of an intermediate fraction, and 425 mg (58%) of *XXV*, m.p. 77·5—79°C (pentane). IR-spectrum ($4{\cdot}96 \cdot 10^{-3}$M, CCl_4): 3624 cm^{-1} (OH). For $C_{11}H_{18}O$ (116·3) calculated: 79·46% C, 10·92% H; found: 79·57% C, 11·12% H.

exo-4-Methoxy-*endo*-5-(*r*-1)tricyclo[4,4,0,$0^{3,8}$]decanecarboxylic Acid (*XIVa*)

A) Dry silver oxide (0·6 g) was added to a solution of *XIXb* (90 mg; 0·43 mmol) and methyl iodide (2·28 g; 16 mmol) in dimethylformamide (0·5 ml) at 0°C, and the mixture was allowed to stand for 48 h at room temperature with intermittent shaking. The mixture was filtered, the solid washed with pentane, the filtrate diluted with water (10 ml), extracted with pentane, the organic layer dried and taken down. Chromatography of the residue on silica gel (50 g, ether–pentane 1 : 3) gave 65 mg (68%) of the ester *XIVb* which was saponified by heating with KOH (70 mg) in 50% aqueous ethanol (0·5 ml) in a sealed ampoule at 100°C for 2 h. The usual work-up procedure followed by crystallisation from light petroleum afforded 55 mg of the acid *XIVa*, m.p. 102—104°C. For $C_{12}H_{18}O_3$ (210·3) calculated: 68·54% C, 8·63% H; found: 68·76% C, 8·53% H.

B) A solution of *Xb* (155 mg) in 2M methanolic sodium methoxide (1·5 ml) was heated in a sealed ampoule to 100°C for 6 h, cooled, diluted with water (15 ml), extracted with ether (3 × 5 ml), dried and the solvent was evaporated. Chromatography of the residue (132 mg; 73%) on silica gel (100 g) using ether–light petroleum (1 : 3) as eluent separated the staring material (4%) from the mixture (90 mg) of two methoxy esters (77% and 19%). The peak of the preponderant methoxy ester had an identical retention time with *XIVb* obtained from *XIXb* in the preceding experiment. This mixture was saponified exactly as described in the preceding preparation. Three crystallisations of the crude mixture of acids afforded pure *XIVa*, m.p. 102—104°C, identical with the acid prepared ad *A* and *C*.

C) A solution of *XVIIIb* (200 mg; 0·95 mmol) in 2M methanolic sodium methoxide (2 ml) was heated to 100°C for 6 h. The isolation procedure was the same and afforded an identical mixture

of methoxy esters (100 mg, 47%) as in the preceding experiment; saponification of this mixture and three crystallisations of the product gave *XIVa*, identical with the specimen prepared under *A* and *B*.

Equilibration Procedures

The equilibration procedures and analytical methods employed were those reported in ref[21]. Except for the pair *XXVI* ⇄ *XXVII* where the former epimer was not available equilibrium was reached from both sides. The equilibration conditions and results are listed in Table I. Chromatographic columns used for the analyses are as follows: for *VII* and *VIII* 5% diglycerol on ground porous tile, for *XIb* and *XIIb* Carbowax 20.000 in 50 m stainless capillary, for *XXIV*—*XXVII* Carbowax 400 or 20.000 in a 50 m glass capillary, for *XVIIIb*—*XXb* poly(butylene glycol adipate) (2·86%) and 1 : 1 mixture of poly(butylene glycol adipate) and 1,2,3,4-tetrakis-(2-cyanoethoxy)-butane on Chromosorb W 100/120 mesh (5·6% w/w), for *XXVIII*—*XXXI* 10% poly(ethylene glycol adipate) on Chromaton 0·20/0·25 mm.

REFERENCES

1. Eliel E. L., Allinger N. L., Angyal S. J., Morrison G. A.: *Conformational Analysis*, Chapter 1. Wiley, New York 1965.
2. Tichý M., Vašíčková S., Arakelian S. V., Sicher J.: This Journal *35*, 1522 (1970).
3. Orahovats A., Tichý M., Sicher J.: This Journal *35*, 838 (1970).
4. Tichý M., Kniežo L.: Tetrahedron Letters *1971*, 1665.
5. Whitlock H. W., jr, Siefken H. W.: J. Am. Chem. Soc. *90*, 4929 (1968).
6. Sicher J., Tichý M.: This Journal *32*, 3687 (1967).
7. Tichý M., Sicher J.: This Journal *33*, 68 (1968).
8. *IUPAC 1968 Tentative Rules, Section E*, IUPAC Information Bulletin No 35, p. 51 (1969).
9. Gauthier J., Deslongchamps P.: Can J. Chem. *45*, 297 (1967).
10. Tichý M., Kniežo L.: Unpublished results.
11. Karplus M.: J. Chem. Phys. *30*, 11 (1959).
12. Karplus M.: J. Am. Chem. Soc. *85*, 2870 (1963).
13. Winstein S., Clippinger E., Howe R., Vogelfanger E.: J. Am. Chem. Soc. *87*, 376 (1965).
14. Benjamin B. M., Ponder B. W., Collins C. J.: J. Am. Chem. Soc. *88*, 1558 (1966).
15. Monson R. S.: Tetrahedron Letters *1971*, 567.
16. Ingold C. K.: J. Chem. Soc. *119*, 329 (1921).
17. Šipoš F., Krupička J., Tichý M., Sicher J.: This Journal *27*, 2079 (1962).
18. Sicher J., Tichý M., Šipoš F.: This Journal *31*, 2238 (1966).
19. Stolow R. D.: J. Am. Chem. Soc. *86*, 2170 (1964).
20. Tichý M., Sicher J.: This Journal *37*, 3106 (1972).
21. Tichý M., Šipoš F., Sicher J.: This Journal *31*, 2889 (1966).
22. Sicher J., Šipoš F., Tichý M.: This Journal *26*, 847 (1961).
23. Sicher J., Tichý M., Šipoš F., Svoboda M., Jonáš J.: This Journal *29*, 1561 (1964).

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