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3,7-DISUBSTITUTED BICYCLO[3.3.1] NONANES—II[1]

SYNTHESIS AND CONFORMATION OF SOME 3,7-DISUBSTITUTED 9-OXOBICYCLO[3.3.1] NONANES

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Abstract—Condensation of pyrrolidine enamines of 4-alkylcyclohexanones with methyl α-(bromomethyl)acrylate affords methyl 7β- and 7α-alkyl-9-oxobicyclo[3.3.1] nonane-3α-carboxylates in a ratio of 3:2. The mechanism of the annelation reaction is discussed. The conformations of the reaction products and their epimers have been studied by means of PMR spectroscopy.

INTRODUCTION

Bicyclo[3.3.1]nonane and some of its derivatives have been shown to exist in a somewhat flattened double-chair conformation (I).[2-7] Introduction of a 3β- or 7β-substituent is not expected to influence this conformation seriously. Substitution at the 3α- and/or 7α-position, however, introduces severe transannular 3,7-interactions and 1,3-diaxial interactions in the double chair conformation. Therefore in these derivatives the rigid chair-boat (II and IV) and the double-boat conformation (III) are assumed to play a major role.[8-16]

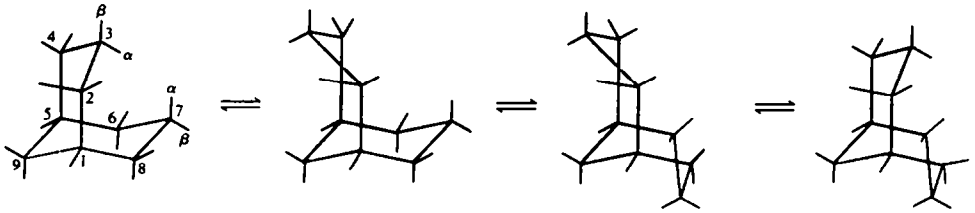
Previously we reported on the synthesis and conformation of some 3α,7α-disubstituted bicyclo[3.3.1]nonanes.[1] The present study deals with the related class of 9-oxobicyclo[3.3.1]nonanes. Here 3,9- and 7,9-hydrogen-hydrogen repulsion in the boat conformers is absent and therefore the energy difference between chair and boat conformations of the rings is expected to be smaller than in the parent ring system. We have performed a PMR conformational study of a number of methyl 7-alkyl-9-oxobicyclo [3.3.1]nonane-3-carboxylates, which were synthesized by means of α,α'-annelation of pyrrolidine enamines of 4-alkylcyclohexanones (1) with methyl β,β'-dibromoisobutyrate (2) (Scheme 1).[17-19]

In view of the results of Lawton *et al.*[19] who investigated the condensation of **1d** with dimethyl γ-bromomesaconate, one should expect methyl 7α-alkyl - 9 - oxobicyclo[3.3.1]nonane - 3α - carboxylates (4) to be the main products. In our hands, however, the major product was always the 3α,7β-epimer (3). In the present paper the mechanism of these reactions is discussed.

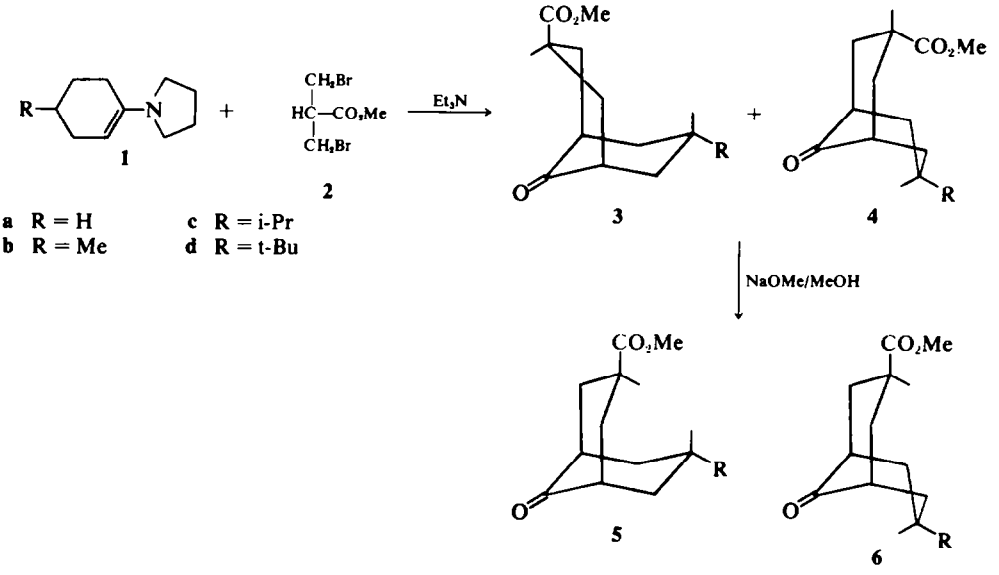
THE ANNELATION REACTION

Configuration of the annelation products. Condensation of compounds **1** with methyl α-(bromomethyl)-acrylate, prepared *in situ* from **2** and Et_3N, afforded mixtures of **3** and **4**, the ratio of which appeared to be independent on the 4-alkyl group in **1** (Table 1).

Treatment of the mixtures obtained with NaOMe-MeOH gave epimerisation towards two other esters (**5** and **6**), showing that **3** and **4** differed only in the position of the alkyl group. Apparently the position of 3-CO_2Me in **3** and **4** is α: epimerisation then results in the more stable 3β-isomers. Further information on the configuration of the esters was obtained by PMR spectroscopy (100 MHz), using the shift reagents Eu(DPM)$_3$ and Eu(FOD)$_3$.[20-22] The various signals were assigned by



I II III IV



SCHEME 1.

Table 1. Annelation of pyrrolidine enamines of 4-alkylcyclohexanones with methyl α-(bromomethyl)-acrylate

Starting compound	Reaction products Yield, %	% 3	% 4
1a (R = H)	85		
1b (R = Me)	89	63	37
1c (R = i-Pr)	81	60	40
1d (R = t-Bu)	89	59	41

the relative shifts, the splitting patterns, and by using double resonance techniques.

The values of the coupling constants (see Table 2) prove that the main products (**3**) are the 3α, 7β-epimers, with the ring containing the 3α-CO_2Me function in the boat conformation and the other ring in the chair conformation, while the minor products (**4**) are the 3α, 7α-epimers in a chair-boat conformation with the ring with the 7-R in the boat conformation. These assignments are in agreement with the results of the epimerisation experiments.

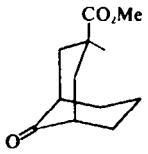
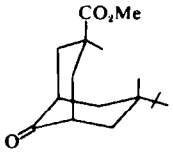
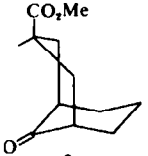
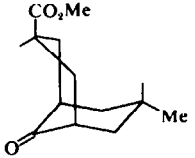
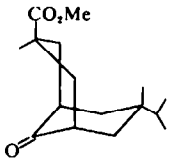
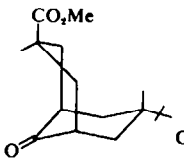
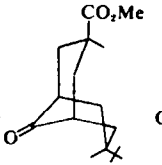
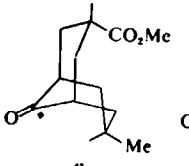
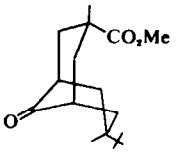
Mechanism. The results of the annelation reactions are not consistent with the mechanism suggested by Lawton *et al.*[19] These authors have shown that the reaction proceeds *via* a C-alkylation-proton transfer-Michael condensation path (*cf* Scheme 2). After alkylation an equilibrium of both *trans* (**7**) and *cis* (**8**) position of R relative to the methylacrylate chain is possible, through a H^+ addition/elimination mechanism. For the Michael annelation to take place, it is obviously necessary that the methylacrylate chain is in a quasi-axial position. The *trans* compound (**7**) affords the 7β-R epimer (**9**), the *cis* compound (**8**) the 7α-R epimer (**10**). During the condensation of **7** a 3-CO_2Me-7-H interaction is introduced, while during the ring closure of **8** the original enamine ring will be forced into the boat conformation (to prevent severe 1,3-diaxial interactions). In view of the observed ratio of the two resulting esters there is no significant preference for one of the reaction paths. Unlike Lawton *et al.*, according to whom the reaction should proceed predominantly *via* **8**, we therefore assume that a boat-like conformation of the original enamine ring is not preferred for ring closure. Protonation of the Michael reaction products (**9**, **10**)* from the least hindered side results in the 3α-CO_2Me derivatives upon hydrolysis (**3**, **4**). During the protonation the ring containing the CO_2Me group might change from a chair into a boat conformation in order to prevent severe interactions with the other cyclohexane ring.

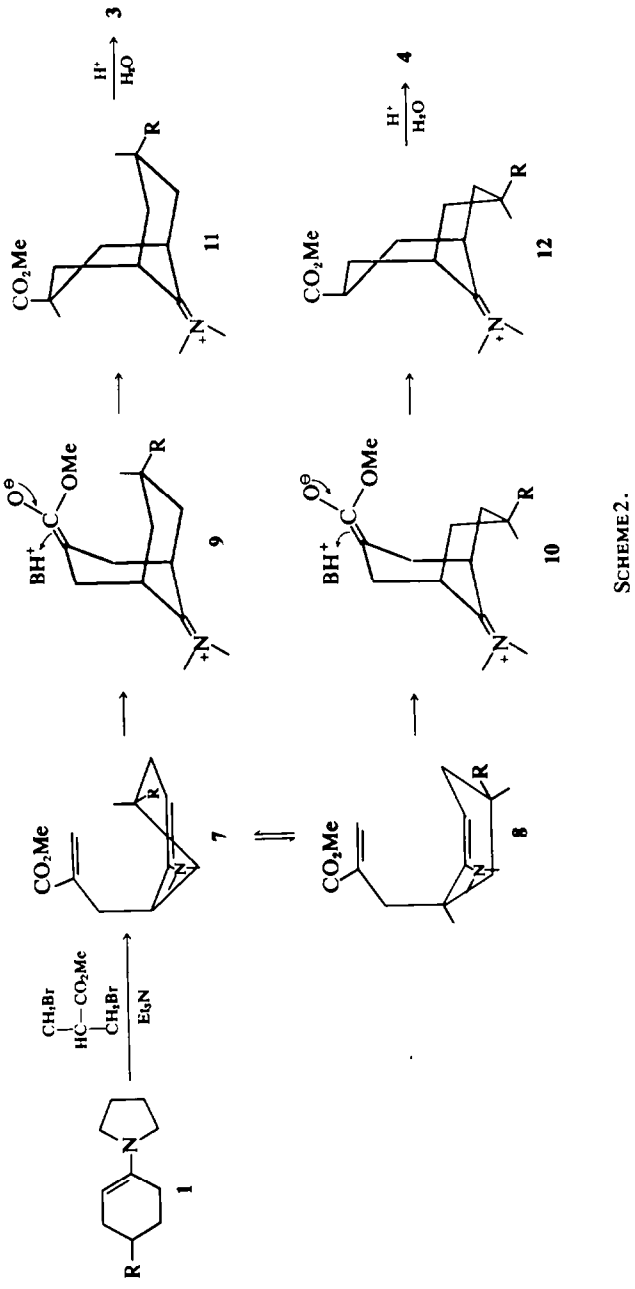
Lawton *et al.* illustrated their mechanism with the condensation of dimethyl γ-bromomesaconate (**13**) and the pyrrolidine enamine of 4-t-butylcyclohexanone (**1d**)[19] (Scheme 3).

These authors identified, by chemical means, the products to be dimethyl 7β-t-butyl-9-oxobicyclo[3.3.1]nonane-2β, 3α-dicarboxylate (**14**) and the corresponding 7α-t-Bu epimer (**15**) (**14**: **15** = 1:9). When repeating this reaction, we obtained two compounds in a ratio of about 5:1. The physical constants of the major isomer were the same as those described by Lawton *et al.*, but con-

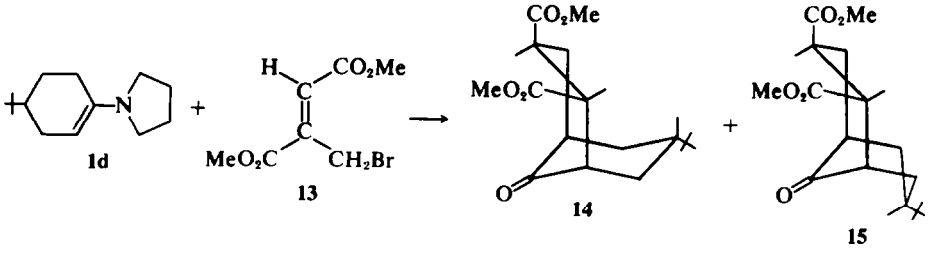
*In contrast to Lawton *et al.*, we assume **9** to be in the double chair conformation. A PMR study of the model compound 3-isopropenyl-9-oxobicyclo[3.3.1]nonane showed that this compound is in the double-chair conformation too.

Table 2. Coupling constants of 3- and 3,7-substituted 9-oxobicyclo[3.3.1]nonanes (± 0·5Hz)

	 5a	 5d	 3a	 3b	 3c	 3d	 6d	 4b	 4d
$J_{1e,2e}$	<3	<3	<3	~2	<3	<3	3–4	<4	<4
$J_{1a,2e}$	4·3	4·2	9	10	9·5	10	3–4	<5	<5
$J_{1e,8e}$	—	<3	<3	<3	2–3	2–3	—	<4	<4
$J_{1a,8a}$	—	3	3	—	3	2·2	—	9·0	8–9
$J_{2e,2a}$	−14·0	−14·0	−14·0	−14·0	−14·0	−14·0	−12·5	−15·5	~−13
$J_{2e,3}$	5·2	5·5	12·5	12·7	13·0	12·5	3·7	<4	<4
$J_{2a,3}$	12·7	12·0	5·5	5·2	5·5	5·5	12·7	6·5	5–7
$J_{4e,4a}$	—	−13·0	−13·0	—	−12·0	−12·0	—	−12·6	−12·0
$J_{6e,7e}$	—	3	3·9	—	—	3·2	—	—	—
$J_{6e,7a}$	—	—	≤3	—	—	—	13·0	13·0	12·7
$J_{6a,7e}$	—	13·0	14	—	13·0	13·2	—	—	—
$J_{6a,7a}$	—	—	≤3	—	—	—	4·2	~4	5·2
$J_{7e,7a}$	—	—	−14·0	—	—	—	—	—	—



SCHEME 2.



SCHEME 3.

trary to the assignment of these authors the structure of this product is actually **14**. This follows from the PMR spectrum, which shows singlets at δ 3·66 (6 H, 2-CO_2Me and 3-CO_2Me), and at δ 0·95 (9 H, t-Bu), a doublet of doublets at δ 3·18 (1 *H*, J = 12·0 Hz and J = 3·7 Hz, $H_{2\alpha}$), and a complex signal at δ 1·5–2·7 (10 H, other ring protons). The splitting pattern of the $H_{2\alpha}$-signal shows that the two CO_2Me groups are *trans* with respect to each other. $Eu(DPM)_3$ was added until the multiplets of H_1, $H_{2\alpha}$, $H_{3\beta}$, $H_{4\alpha}$, $H_{4\beta}$, and H_5 were separated. The signal of H_5 is a broad doublet (J = 10 Hz), which changed into a broad singlet upon irradiation of $H_{4\beta}$. Therefore the dihedral angle between H_5 and $H_{4\beta}$ will be near 0°, proving that the ring containing the CO_2Me groups is in the boat conformation. Since the couplings between H_5 and $H_{6\alpha}$ and $H_{6\beta}$ are small, the other ring is in the chair form. The signal of H_1 is a broad singlet, confirming that a chair-boat conformation is involved. This is only possible if the 7-t-Bu group is in the β-position, showing that the major isomer is **14**. With the aid of double resonance techniques the following proton-proton coupling constants were determined: $J_{2\alpha 1}$ = 3·7; $J_{2\alpha 3\beta}$ = 12·0; $J_{3\beta 4\alpha}$ = 12·0; $J_{3\beta 4\beta}$ = 5·0–5·5; $J_{4\beta 5}$ = 10; $J_{6\alpha 6\beta}$ = −12·0 Hz. All values are in agreement with the proposed configuration and conformation.

CONFORMATION OF THE ANNELATION PRODUCTS AND THEIR EPIMERISATION PRODUCTS

The conformations of the annelation products (**3** and **4**) and their epimers (**5** and **6**) were studied by means of PMR spectroscopy (100 MHz). Spectra with various amounts of the shift reagents $Eu(DPM)_3$ or $Eu(FOD)_3$[20–22] were recorded. From the spectra with optimal separation between the various multiplets the coupling constants were obtained by first-order analysis. No influence of the ratio added complex/substrate on the coupling constants could be detected. We therefore assume that in these cases the shift reagent has no significant influence on the coupling constants or on the geometry of the substrate.[23] Excellent straight lines were obtained, when the chemical shifts of the CO_2Me protons were plotted *vs* the chemical shifts of the various ring protons with increasing amounts of shift reagent.[1,24] The slope of these lines is dependent on the distance of the proton in question to the Eu^{3+}-ion which is coordinated to the 9-oxo function (and less strongly to the 3-CO_2Me group[24]). The signals were assigned by means of the splitting patterns, mutual decoupling experiments and the slopes mentioned. The coupling constants measured are given in Table 2.

Methyl 7β-t-butyl-9-oxobicyclo[3.3.1]*nonane-3β-carboxylate* (**5d**). The magnitude of the vicinal coupling constants in methyl 9-oxobicyclo[3.3.1]nonane-3β-carboxylate (**5a**) and the corresponding 7β-t-Bu compound (**5d**) (Table 2) proves, as should be expected from literature data,[2–7] that these compounds adopt the double-chair conformation. A substantial contribution of a chair-boat conformation in **5a** can be excluded by comparison of the coupling constants of compounds **5a** and **5d**. The latter compound can be assumed, *a priori*, to exist in the double-chair conformation, since in the chair-boat conformation there would be a considerable flagpole interaction.

From the values of $J_{2\alpha 3}$ and $J_{2\beta 3}$ it can be seen that the cyclohexane ring carrying the CO_2Me group is distinctly flattened in **5a** and **5d**. The corresponding coupling constants in methyl *trans*-4-t-butylcyclohexanecarboxylate were found, with the aid of the same procedure, to be 3·7 and 12·0. About the same values have been obtained by Remijnse *et al.*[25] for t-butylcyclohexane and cyclohexane.

Assuming tetrahedral HCH angles, it can be calculated by means of the Karplus equation[26] that the dihedral angle between H_3 and $H_{2\alpha}$ is about 50°. This value was also calculated from the X-ray data of Brown *et al.*[3] for 1-*p*-bromobenzenesulphonoxymethyl-5-methylbicyclo[3.3.1]nonan-9-ol.

Methyl 7β-alkyl-9-oxobicyclo [3.3.1]*nonane-3α-carboxylates* (**3**). The coupling constants of the methyl 7β-alkyl-9-oxobicyclo[3.3.1]nonane-3α-carboxylates (**3**) unambigiously prove that these compounds exist in the chair-boat conformation, with the ring with the 3α-CO_2Me in the boat form. Since there is no difference in coupling constants between **3a** and the corresponding 7β-alkyl derivatives (**3b-d**), the other chair-boat conformation can be ignored for **3a**. In compounds **3b-d** this conformation is unfavorable due to the flagpole interac-

tion between the alkyl group and the 9-oxo function.

The magnitudes of the vicinal coupling constants in the ring holding the 3α-CO_2Me group differ from those expected for an ideal rigid boat cyclohexane ($J_{2\alpha3}$ = 13·0 Hz, $J_{2\beta3}$ = 3·6 Hz,[25] and $J_{12\beta}$ = 12–13 Hz[27]). Probably the boat is flattened at the 3-position.

The coupling constants of the protons in the chair ring have almost the same values as those in cyclohexanes,[25] showing that this ring has about the normal cyclohexane geometry.

Methyl 7α-t-butyl-9-oxobicyclo [3.3.1]*nonane-3β-carboxylate* (**6d**). Molecular models leave no doubt that the ring containing the 7α-t-Bu substituent should be in the boat conformation, whereas extrapolation of previous results shows that the other ring has to possess the chair conformation. This is confirmed by the PMR data. Furthermore the coupling constants show that the chair part has about the ideal geometry. The boat ring is less flattened than the boat ring in compounds **3**. Apparently non-bonding interactions between the t-Bu group and the 6- and 8-protons oppose flattening[25].*

Methyl 7α-alkyl-9-oxobicyclo [3.3.1]*nonane-3α-carboxylates* (**4**). The coupling constants of **4b** and **4d** in the presence of $Eu(FOD)_3$ (Table 2) show that these compounds exist predominantly in the chair-boat conformation with the ring containing the alkyl group in the boat form. Since we were not able to assign the signals for $H_{2\alpha}$ and $H_{2\beta}$ with certainty, the high value of one of the couplings J_{23} can be explained either by a strong flattening of the boat ring or by a contribution of other conformations *e.g.* the double-boat and in **4b** the other chair-boat.

When plotting the chemical shifts of the various protons *vs* the chemical shifts of the CO_2Me-protons at different substrate/$Eu(FOD)_3$ ratios the usual straight lines were not obtained. Therefore it is doubtful whether the shift reagent has no influence on the conformations in these cases.

The IR spectrum of **4d** showing strong absorption at 1452 cm^{-1} supports a major role of the chair-boat conformation. This band has been shown to be absent in cyclohexane derivatives which occur in a non-chair conformation.[28] Moreover the pK_a* of the corresponding carboxylic acid (Table 3) is rather high compared with the pK_a*'s of the acids corresponding to **3b** and **3d**.† This is in agreement with a contribution of the chair-boat, since in this conformation steric hindrance of the carboxylate anion will cause acid weakening.[29]

Table 3. pK_a*-Values of 7 - R - 9 - oxobicyclo [3.3.1] nonane - 3α - carboxylic acids in 50% ethanol–water at 25°

7—R	pK_a*
H	5·43
β-Me	5·38
β-i-Pr	5·43
β-t-Bu	5·42
α-t-Bu	5·78

Molecular models leave no doubt that in **4d** the ring with the 7-t-Bu group is in the boat conformation. Appleton *et al.* have estimated the enthalpy difference between double-chair and chair-boat conformers in bicyclo[3.3.1]nonane, apart from transannular ring strain, to be *ca* 5·7 kcal/mole.[11] We consider this to be a good approximation of the enthalpy difference between chair-boat and double-boat. In the 9-oxo derivatives the enthalpy of the double-boat conformer will be lowered by *ca* 1·1 kcal/mole,[30] since the flagpole interaction is absent here. Introduction of a 3α-CO_2Me group would give, according to the estimations of Appleton *et al.*[11] an increment of *ca* 3·5 kcal/mole of the enthalpy of the chair-boat conformer. Therefore the enthalpy difference between the chair-boat and the double-boat conformation in **4d** should be *ca* 1·1 kcal/mole (5·7–1·1–3·5) in favor of the former conformer.‡ In agreement with the experimental data this rough estimate shows that a slight preference for the chair-boat conformation in **4d** might be expected.

EXPERIMENTAL

The PMR spectra were obtained with a Varian XL-100-15 NMR spectrometer system equipped with a V-4415 universal probe and a V-4421 gyrocode decoupler unit.

Spectra were recorded at 39° in CCl_4 soln. Chemical shifts are given in ppm (δ) relative to TMS. CCl_4 was stored over molecular sieve 4A. The lanthanide shift reagents $Eu(DPM)_3$ and $Eu(FOD)_3$ were obtained from Merck and sublimed at 180°/0·3 mm before use.

Elemental analyses were performed by Messrs. M. van Leeuwen and M. A. Hoefnagel and were correct within 0·2% (absolute).

Annelation reactions, general procedure. To a stirred boiling soln of 0·052 mole freshly distilled pyrrolidine enamine of the cyclohexanone and 5·05 g (0·05 mole) Et_3N in 60 ml MeCN (dried over molecular sieve 3A) was added dropwise in 1 hr a soln of 13·00 g (0·050 mole) methyl β,β'-dibromoisobutyrate in 40 ml MeCN. Then the mixture was boiled under reflux for 2 hr. After addition of

*X-ray analysis even showed puckering of the boat ring in 9-benzoyl-3α-bromo-9-azabicyclo [3.3.1] nonane-2-one.[15]

†The pK_a*-value of the monocyclic parent compound 4-oxocyclohexanecarboxylic acid was found to be 5·41 suggesting an important contribution of boat conformations to the conformational equilibrium of this compound. This is supported by the magnitudes of the coupling constants measured in methyl 3, 3, 5, 5 - tetradeutero - 4 - oxocyclohexanecarboxylate (J_{12} = 9·32 Hz, $J_{12'}$ = 4·20 Hz, and $J_{22'}$ = − 13·8 Hz).

‡Since twisting in the boat-rings creates a serious 2,6-interaction, it may be doubted whether the double-twist conformation is populated to any extent.

5 ml 5% HOAc the mixture was boiled for another hour. The resulting soln was diluted with 125 ml H_2O and extracted with five 60 ml portions ether. The ethereal layers were washed with three 60 ml portions 2N HCl, two 60 ml portions sat $NaHCO_3$ aq, and two 60 ml portions sat NaCl aq, and dried over $MgSO_4$. The solvents were evaporated under vacuum yielding the crude ester mixture.

The composition of the products was determined *via* integration of the CO_2Me signals in the PMR spectra and/or by GLC analysis.

It was observed that longer reaction times (*cf* Ref 20) did not influence the yield or the composition of the products.

Epimerisation experiments, general procedure. To a soln of 75 mg Na in 100 ml MeOH was added 1 g ester. After boiling for 6 hr the mixture was poured onto 100 ml 1N HCl. The dispersion obtained was extracted several times with ether. The ether soln was washed with water and dried over $MgSO_4$. After filtration the solvent was evaporated off and the ester mixture was analysed by GLC and PMR.

Methyl 9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**3a**), b.p. 165–166°/17 mm (*cf.* Ref 20); m.p. 41–42°; PMR: δ 3·62 (3H, s); 1·4–2·6 (13H). The corresponding acid was obtained by hydrolysis of **3a** in 2N KOH; m.p. 134–135° from light petroleum-EtOAc.

Methyl 7β-methyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**3b**). The crude annelation product of 4-methylcyclohexanone (9·90 g) was hydrolysed by boiling with 2N KOH to the acid; m.p. 102·5–103° (from light petroleum-EtOAc). Esterification with CH_2N_2 yielded the Me ester; PMR: δ 3·67 (3H, s), 1·00 (3H, d: J = 6·5 Hz), 1·2–2·8 (12H).

Methyl 7α-methyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**4b**). From the mother liquor of the recrystallisation of **3b** the solvent was evaporateu off and the residue was recrystallised from light petroleum-EtOAc and then esterified with CH_2N_2. After evaporation of the solvent the residue was recrystallised from light petroleum to yield pure **4b**; m.p. 56·5–57·5°; PMR: δ 3·74 (3H, s), 0·86 (3H, d: J = 6 Hz), 1·2–2·8 (12H).

Methyl 7β-isopropyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**3c**). This ester was obtained analogously to compound **3b**, m.p. acid 122–123°, Ester; PMR: δ 3·60 (3H, s), 0·93 (6H, d: J = 7 Hz) 0·9–3·0 (13H).

Methyl 7α-isopropyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**4c**). The mother liquor of the recrystallisation of **3c** was recrystallised from light petroleum-EtOAc and sublimed to pure 7α-isopropyl-9-oxobicyclo[3.3.1] nonane-3α-carboxylic acid; m.p. 91–93°. Esterification with CH_2N_2 yielded the Me ester **4c**; PMR: δ 3·70 (3H, s), 0·82 (6H, d: J = 7 Hz), 1·0–2·7 (13H).

Methyl 7α-t-butyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**4d**). The crude annelation product of 4-t-butylcyclohexanone was distilled (b.p. 128–130°/0·5 mm) and then recrystallised several times from light petroleum and sublimed to pure **4d**; m.p. 81·5–82°; PMR: δ 3·72 (3H, s), 0·83 (9H, s), 1·11 (1H, t of t: J = 12·7 and 5·0 Hz), 1·6–2·7 (11H). The corresponding acid was obtained by KOH hydrolysis of **4d**; m.p. 113–113·5° (from light petroleum).

Methyl 7β-t-butyl-9-oxobicyclo[3.3.1]*nonane-3α carboxylate* (**3d**). The mother liquor of the recrystallisation of **4d** was hydrolysed with 2N KOH as described. The mixture of acids obtained was recrystallised several times from light petroleum-EtOAc to yield pure 7β-t-butyl-9-oxobicyclo[3.3.1]nonane-3α-carboxylic acid; m.p. 180·5–181°. This acid was esterified with CH_2N_2 to **3d**; PMR: δ 3·63 (3H, s), 0·93 (9H, s), 1·4–2·5 (12H).

Methyl 9-oxobicyclo[3.3.1]*nonane-3β-carboxylate* (**5a**). Compound **3a** was epimerised according to the general procedure. The ester obtained was hydrolysed with 2N KOH as described. The acid was recrystallised from light petroleum-EtOAc and sublimed; m.p. 152–152·5°. Esterification of this acid with CH_2N_2 yielded pure **5a**, PMR: δ 3·63 (3H, s), 3·36 (1H, m), 2·39 (2H), 1·9–2·3 (10H).

Methyl 7β-t-butyl-9-oxobicyclo[3.3.1]*nonane-3β-carboxylate* (**5d**). This compound was synthesised by epimerisation of **3d**, according to the general procedure; m.p. 96·5–97° (from light petroleum); PMR: δ 3·63 (3H, s), 0·90 (9H, s), 3·39 (1H, m), 2·36 (2H), 1·6–2·6 (9H).

Methyl 7α-t-butyl-9-oxobicyclo[3.3.1]*nonane-3β-carboxylate* (**6d**). Ester **4d** was epimerised according to the general procedure. The epimer was recrystallised from light petroleum and sublimed; m.p. 95–95·5°; PMR: δ 3·64 (3H, s), 0·93 (9H, s), 3·08 (1H, m), 1·12 (1H, m), 1·5–2·6 (10H).

Dimethyl 7β-t-butyl-9-oxobicyclo[3.3.1]*nonane-2α,-3α-dicarboxylate* (**14**). The crude annelation product of the pyrrolidine enamine of 4-t-butylcyclohexanone and dimethyl γ-bromomesaconate was titruated with ether. The solid diester was recrystallised from light petroleum-EtOAc; m.p. 128·5–129°; PMR: δ 3·66 (6H, s), 0·95 (9H, s), 3·18 (1H, d of d: J = 12·0 and 3·7 Hz), 1·5–2·7 (10H).

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