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A tricycloheptane product in cationic rearrangements

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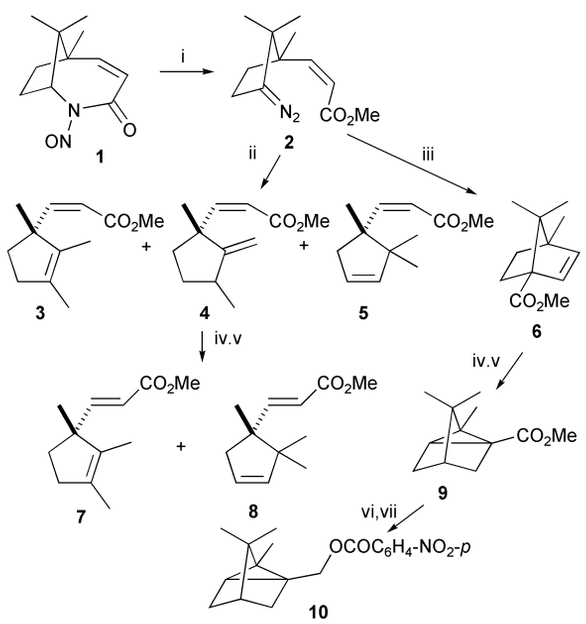
The bicycloheptene **6** rearranged in acid to give the tricycloheptane **9**, as shown by an X-ray crystal structure determination of the *p*-nitrobenzoate **10** derived from it. Earlier results in the literature had already indicated that this isomer was the thermodynamic sink. This apparently crowded structure, with its three contiguous quaternary centres, is, nevertheless, lower in energy than other accessible but less crowded structures, because of electronic stabilisation of the more substituted cyclopropane ring conjugated to the ester group.

Introduction

In 1964, at an early stage in Eschenmoser's and Woodward's synthesis of vitamin B_{12}, one of us prepared the ester **7** by the sequence illustrated in Scheme 1.[1] The bicyclic ester **6** was a by-product derived from the diazoalkane **2**, before the addition of the sulfuric acid. The structure of this by-product and the synthetic possibilities it suggested were the subjects of a subsequent investigation,[2] which identified it as the first example of a reaction between a diazoalkane and an ester that matched the better known reaction of diazoalkanes with ketones.

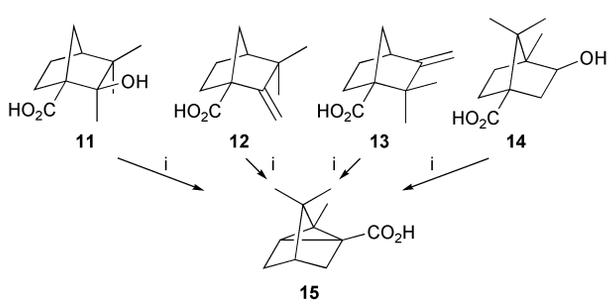


Scheme 1 *Reagents and conditions:* i, NaOMe, MeOH, 0 °C, 1.25 h; ii, H_2SO_4, H_2O; iii, spontaneously over the 1.25 h in MeOH, before the mixture was added to the H_2SO_4; iv, NaOMe, MeOH, reflux, 48 h; v. TsOH, C_6H_6, reflux, 21 h; vi, $LiAlH_4$. Et_2O, rt, 1 h; vii, $ClCOC_6H_4$-NO_2-*p*, Py, 0 °C, 1 h.

In the original work, the mixture of all four products **3**–**6** was refluxed with sodium methoxide in methanol, in order to convert the *cis* α,β-unsaturated esters **3**–**5** into their *trans* esters, and then refluxed with toluenesulfonic acid in benzene for 21 hours, during which treatment the *trans* ester derived from the *cis* ester **4** gave the desired ester **7**. During this reflux with the toluenesulfonic acid, the bicyclic ester **6** rearranged into a tricyclic ester, the structure of which is the subject of this paper. The esters were separated by fractional distillation on a spinning-band column to give pure samples of the major product **7** and the new ester derived from the bicyclic ester **6**.

In 1964, we did not know the structure of the ester **6**, and consequently had no idea what the structure of its rearrangement product might be. We investigated the structure at that time only briefly. It was an isomer, it had no protons attached to trigonal centres, it was optically inactive, and reduction with lithium aluminium hydride gave an alcohol, in which the methylene protons showed an AB pattern with no further coupling. Not knowing the structure of its precursor **6**, and with no further information easily available, the structure of this compound remained a mystery until now, when the ease with which an X-ray crystal structure can be determined has made it possible for us to assign the structure **9**, derived from that of its derivative, the *p*-nitrobenzoate **10**. The crystal structure also showed that, in addition to being optically inactive, the *p*-nitrobenzoate **10** and, therefore. the ester **9** were racemic.

Two questions presented themselves: what is the pathway for the cationic rearrangement **6** ⟶ **9**, and why is the ester **9** the thermodynamic product, when several less crowded isomers are reasonably accessible? Hoyer reported in 1954 that the corresponding acid **15**, which he called *dicadisäure*, is the product of acid-catalysed rearrangements of any of the acids **11**–**14** (Scheme 2).[3] The ester **9** and the acid **15** are evidently sitting in deep wells on the energy surface, in spite of their having three contiguous quaternary centres.



Scheme 2 *Reagents and conditions:* i, 10% H_2SO_4 in H_2O, reflux, few h.

A short and reasonable pathway for the formation of the enantiomer of the ester **9** from the ester **6** is shown in Scheme 3, which identifies a well-precedented 1,3-hydride shift to account for the formation of both enantiomers of the ester **9**.

The fate of the *trans* ester **8** during the treatment with toluenesulfonic acid is uncertain. GC analysis indicated that it was largely consumed during the 21 hour reflux, and the mass balance was closer to suggesting that, rather than being converted into the desired ester **7**, it was being converted into the ester **9**. A reasonable pathway exists for this transformation, including the racemisation, but we were unable to isolate pure ester **8**, and could not check the conversion directly.

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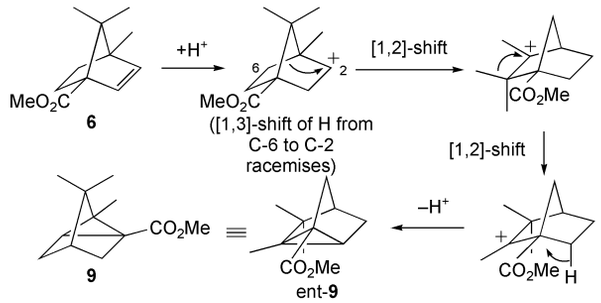

Scheme 3

That leaves the intriguing question of why the congested ester **9** should be thermodynamically favoured over several plausible, but superficially less congested, isomers **16**–**20**. We suggest that it is related to the well known property of cyclopropanes in which they resemble alkenes. We calculated the relative energies for six tricyclic isomers at the B3LYP/6-31G** level,[4] with the results shown in Fig. 1. The isomer **9**, in the conformation **9a** with the carbonyl group pointing up, reassuringly has the lowest energy.

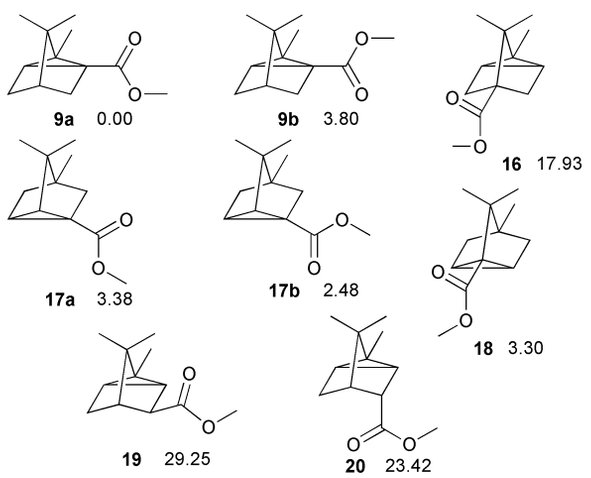

Fig. 1 Relative energies in kJ mol^{-1} of isomeric tricyclic esters $C_{12}H_{18}O_2$.

This result is consistent with the three membered ring having, like a double bond, a thermodynamic preference to be both conjugated and substituted. This is illustrated by the isodesmic reactions **A**–**F** (Fig. 2). **A** and **B** show that esters have a thermodynamic preference to be adjacent to double bonds and cyclopropanes, and that the effect is larger for cyclopropanes. Similarly, **C** and **D** show both double bonds and cyclopropanes benefit from methyl substitution. This preference is slightly increased by the presence of an ester on the far side of the ring (**E**), and reduced if the ester is on the same side (**F**). These results are all consistent with the thermodynamic preference calculated for the isomer **9a**.

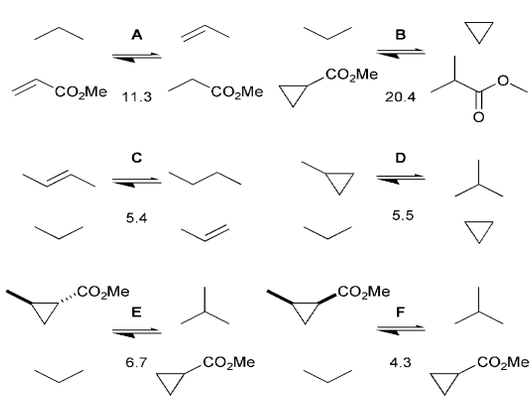

Fig. 2 Isodesmic reactions; energies in kJ mol^{-1}.

Experimental

Methyl 2,7,7-trimethyltricyclo[2.2.1.0^{2,6}]heptan-2-carboxylate 9

The tricyclic ester **9** (8.4 g)[1] was redistilled on the spinning band column (bath temperature 127 °C, column temperature 85 °C, drip ratio 1 : 20), collecting fractions over 12 h. The second fraction (3.45 g) was a pure sample of the ester, bp 101–103 °C/16 mmHg (lit.[3] 100–101 °C/17 mmHg); $\nu_{max}(CCl_4)$/cm^{-1} 1720 (CO); δ_H(60 MHz; CCl_4) 3.55 (3 H, s, OMe), a methylene envelope, 1.12 (3 H., s, Me) and 0.83 (6 H, s, 2 × Me).

2,7,7-Trimethyltricyclo[2.2.1.0^{2,6}]heptan-2-carboxylic acid 15

The ester (2.6 g) was refluxed in methanol (30 ml) with aqueous sodium hydroxide (10%, 10 cm^3) for 3 h, and the methanol distilled off under reduced pressure. The residue was cooled to room temperature and washed with ether. The aqueous layer was acidified with hydrochloric acid (3 mol dm^{-3}) and extracted with ether. The ether was dried (Na_2SO_4) and evaporated, to give the acid (1.93 g, 83%) as prisms, mp 135–136° (from n-hexane) (lit.[3] mp 139–140 °C, from AcOH); $\nu_{max}(CCl_4)$/cm^{-1} 3300–2500 (br, OH) and 1675; δ_H(60 MHz; CCl_4) no absorption at lower field than δ 2.1, 1.3 (3 H, s, Me) and 0.9 (6 H, s, 2 × Me); $[\alpha]^{25}$(*c*. 10 in EtOH) no rotation between 365 and 589 nm (Found: C, 73.33; H, 8.99. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%).

2,7,7-Trimethyltricyclo[2.2.1.0^{2,6}]heptan-2-ylmethyl *p*-nitrobenzoate 10

The acid (100 mg) was added to a solution of diazomethane in ether (25 cm^3) and the ether evaporated. The residue, which showed negligible rotation, was stirred with lithium aluminium hydride (0.1 g) in ether (10 cm^3) at room temperature for 1 h. Water was added until the inorganic material settled, the ether was decanted off, and evaporated to give the alcohol as an oil; δ_H(60 MHz; CCl_4) 3.65 (2 H, s CH_2O), 2.78 (1 H, s, OH), 1.03 (3 H, s, Me), 0.83 (6 H, s, 2 × Me) and 0.70 (1 H, m, cyclopropane-H), which was stirred with *p*-nitrobenzoyl chloride (0.45 g) in pyridine at 0 °C for 1 h. Water and ether were added, the aqueous layer was washed with aqueous acid, and the organic layer evaporated to give the *p*-nitrobenzoate (0.58 g, 89%), as leaflets, mp 125–127 °C (from MeOH); $\nu_{max}(CCl_4)$/cm^{-1} 1720 (CO), 1610 (Ar) and 1535 (NO_2); δ_H(60 MHz; CCl_4) 8.21 (4 H, m. ArHs); 4.8 (1 H, d, *J* 11, OCH_AH_B), 4.3 (1 H, d, *J* 11, OCH_AH_B), 1.15 (3 H, s, Me), 0.91 (3 H, s, Me) and 0.90 (3 H, s, Me); $[\alpha]^{23}$ (*c*. 1.4 in $CHCl_3$) 0 at all wavelengths between 436 and 589 nm (Found: C, 66.71; H, 6.63; N, 4.52. $C_{18}H_{21}NO_4$ requires: C, 68.55; H, 6.71; N, 4.44%).

Crystal data for 10. $C_{18}H_{21}NO_4$, *M*=315.36, triclinic, space group $P\bar{1}$, *a* = 7.0666(4), *b* = 7.0975(4), *c* = 18.3293(13) Å, *U* = 816.98(9) Å^3, *Z* = 2, μ(Mo-Kα) = 0.091 mm^{-1}, 7013 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 2762 unique (R_{int} = 0.068); R_1 = 0.11, wR_2 = 0.267 [I>2σ(I)]. The structure was solved with *SHELXS-97* and refined with *SHELXL-97*.[5] CCDC reference number 216824. See http://www.rsc.org/suppdata/ob/b3/b309329h/ for crystallographic data in .cif or other electronic format.

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