Steric Effects in Five-membered Rings. Part 7.[1,2] Relative Stabilities of Cyclopentane-1,3-dicarboxylate Diesters

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Base-catalysed *cis–trans* equilibria for dimethyl, diethyl, and methyl ethyl cyclopentane-1,3-dicarboxylates were established at several temperatures and solvents. Thermodynamic parameters were calculated thereof and conformational analytical implications are discussed, using a new approach for assessing entropy effects.

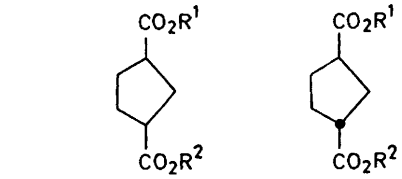
We are looking into the stereochemical and conformational behaviour of 1,3-disubstituted cyclopentane derivatives.[1] The rationale of this choice was to minimize spurious intersubstituent (1,2) steric interference and thus to be able to concentrate on the conformational analysis of the cyclopentane ring. The latter constitutes a rather difficult and sometimes frustrating problem due mainly to the inherent mobility of the five-membered ring.[3]

In this framework we undertook a co-ordinated investigation of physical properties (n.m.r. spectroscopic analysis, dipole moments, i.r. and Raman analysis) of epimeric pairs of 1,3-disubstituted cyclopentanes and their chemical behaviour, *e.g.* their relative stabilities.

We present here the results of a variable temperature study of base-catalysed equilibria between *cis*- and *trans*-dimethyl, diethyl, and methyl ethyl cyclopentane-1,3-dicarboxylates. This enabled us to derive, for the first time from a systematic chemical study, thermodynamic function differences between diastereoisomeric 1,3-substituted cyclopentanes and to dissect them into enthalpy and entropy contributions.

Two simple [equations (1) and (2)] and one complex [equation (3)] equilibria were studied (see Scheme 1). Obviously, the latter also contains equations (1b) and (2b) and thus offers an excellent check of the reliability of the results.

The calculated thermodynamic parameters are collected in Table 1. The experimental results are given in Supplementary Publication No. SUP 21847 (10 pp., 1 microfiche) † and in the plots in Figures 1—3 and represent averages of 3—4 runs at each of five temperatures over a range of *ca.* 40 °C, with at least two equilibria in each case approached from both directions. In processes (1a) and (2a) (MeO^-- or EtO^-- catalysed) the concentrations were 0.2M in ester and 1.0M in catalyst, whereas in processes (1b), (2b), and (3) (Bu^tO^-- catalysed) the concentrations were 2.0M in ester and 0.10—0.16M in catalyst. The extent to which equilibria are affected by catalyst concentrations was examined for equations



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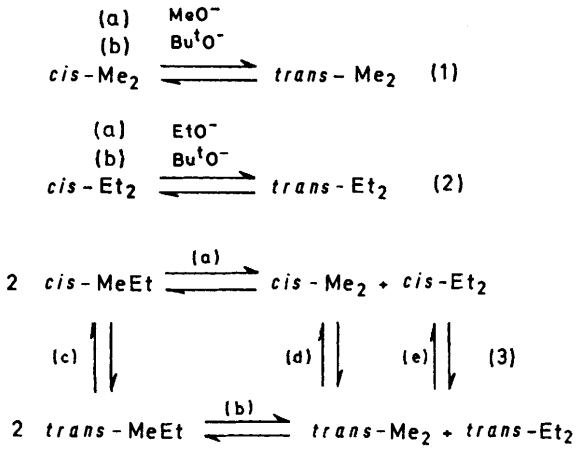
$R^1 = R^2 = Et$
$R^1 = Me, R^2 = Et$



SCHEME 1 The epimerization equilibria studied

† For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue.

[1] Part 6, P. S. Wechsler and B. Fuchs, *J.C.S. Perkin II*, 1976, 943.

[2] Taken from the Ph.D. Thesis of P. S. Wechsler, Tel-Aviv University, 1974.

[3] (*a*) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Wiley, New York, 1966, p. 200; (*c*) C. Altona, 'Conformational Analysis, Scope and Present Limitations,' ed. G. Chiurdoglu, Academic Press, New York, 1971, p. 1; (*c*) B. Fuchs, *Topics Stereochem.*, in the press.

(1a) and (2a) and seen not to present a serious problem in the process of interpretation of the results.

The equilibrium mixtures were analysed by g.l.c. using disc integration or planimetry and the thermodynamic functions were calculated by a least squares analysis. Processes (3a and b) are transesterification equilibria. Their constants could also be determined, which constituted an interesting supplement.

The dimethyl and diethyl esters were prepared from the known norcamphoric and isonorcamphoric acids. The *cis*-methyl ethyl ester was obtained by starting with norcamphoric anhydride in a sequence consisting of reaction with ethanol to give the half (ethyl) ester followed by diazomethane treatment. The *trans*-methyl ethyl ester was prepared from isonorcamphoric acid which was transformed into the monosodium salt. The latter was esterified with diazomethane and the half ester thus obtained was esterified using 1-ethyl-3-*p*-tolyltriazene.

All six esters were fully characterized and their physical data are given in Table 2. The relative retention times on a SAIB column are seen in the sample gas-chromatogram depicted in Figure 4.

TABLE 1

Thermodynamic parameters of equilibrium reactions involving esters of epimeric cyclopentane-1,3-dicarboxylic acids

Equilibrium	Catalyst–solvent	$\Delta H°$/kcal mol^{-1}	$\Delta S°$/cal mol^{-1} K^{-1}	$\Delta G°_{322}$/kcal mol^{-1}
Me_2 (1a) [a]	MeONa–MeOH	0.07 ± 0.08	0.5 ± 0.3	−0.08 ± 0.02
Et_2 (2a)	EtONa–EtOH	0.13 ± 0.07	0.7 ± 0.2	−0.10 ± 0.01
Me_2 (1b)	But^{t}OK–But^{t}OH	0.08 ± 0.09	1.0 ± 0.2	−0.23 ± 0.01
Et_2 (2b)	But^{t}OK–But^{t}OH	−0.01 ± 0.09	0.8 ± 0.3	−0.27 ± 0.01
Me_2 (3d)	But^{t}OK–But^{t}OH	0.06 ± 0.08	1.0 ± 0.2	−0.25 ± 0.01
Et_2 (3e)	But^{t}OK–But^{t}OH	−0.01 ± 0.07	0.7 ± 0.2	−0.24 ± 0.01
MeEt (3c)	But^{t}OK–But^{t}OH	0.07 ± 0.07	1.0 ± 0.2	−0.24 ± 0.01
cis-Transesterification (3a)	But^{t}OK–But^{t}OH	0.19 ± 0.14	−2.1 ± 0.4	0.86 ± 0.01
trans-Transesterification (3b)	But^{t}OK–But^{t}OH	0.0 ± 0.12	−2.7 ± 0.4	0.86 ± 0.01

[a] See Scheme 1.

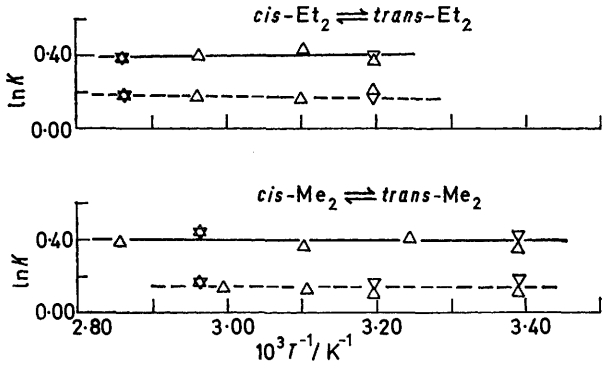


FIGURE 1 Graphs of ln$K$ *versus* $1/T$ for equilibria (1a) and (2a) (broken lines) and (1b) and (2b) (full lines)

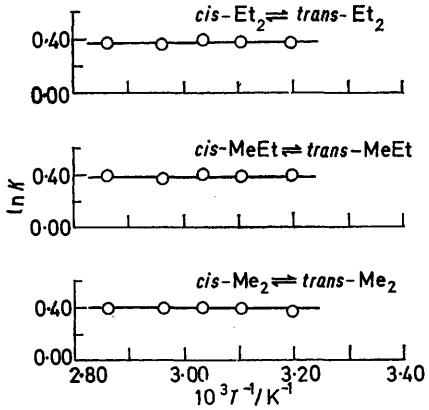


FIGURE 2 Graphs of ln$K$ *versus* $1/T$ for equilibria (3c—e)

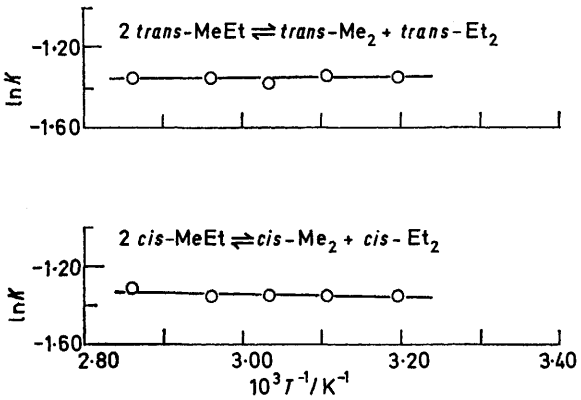


FIGURE 3 Graphs of ln$K$ *versus* $1/T$ for equilibria (3a and b)

TABLE 2

Physical properties of the stereoisomeric cyclopentane-1,3-dicarboxylates and -dicarbonitriles

Ester	B.p. (°C) [p/Torr]	Refractive index n_D (t/°C)	D_4 g/cm^{-3} (t/°C)
cis-Dimethyl [a]	140 [25] 144 [30]	1.449 76(28)	1.114(28)
trans-Dimethyl [a]	130 [25]	1.457 83 (20), 144 850(28)	1.115(28)
cis-Diethyl [a]	152 [25]	1.448 31(20) 144 002(28)	1.073(25)
trans-Diethyl [a]	142 [25]	1.439 28(28)	1.068(25)
cis-Ethyl methyl	143 [25]	1.445 23(28)	1.093(25)
trans-Ethyl methyl	135 [25]	1.444 67(28)	1.090(25)
cis-Nitrile	195 [28]	1.468 02(25)	1.036(25)
trans-Nitrile	178 [25]	1.468 10(25)	1.038(25)

[a] Known compound.

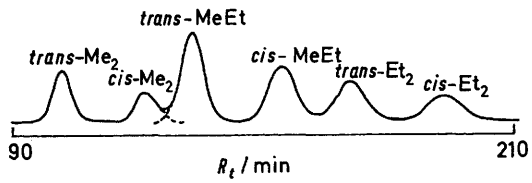


FIGURE 4 Sample of a g.l.c. chromatogram as obtained from equilibrium (3)

DISCUSSION

There are two contexts in which the results ought to be discussed, relative stabilities and conformation of substituted cyclopentanes, and those of analogous cyclohexanes.

1,2-Disubstituted cyclopentanes exhibit relatively large energy differences between corresponding stereoisomers in favour of the *trans*-isomers. Thus for *cis* ⇌ *trans*-1,2-dimethylcyclopentane $\Delta G°$ lies in the range −1.73 to −1.94 kcal mol^{-1} [4,*] and similar values have been found for various other 1,2-dialkyl derivatives.[5] The same trend has been found for 1,2-dimethoxycarbonyl-[6] and even more accentuated for 1,2-diphenyl-cyclopentanes.[7] There is little doubt that this preference for the *trans*-geometry stems from trivial substituent steric interference and not from ring conformational effects, a fact which lends support to our approach in this and previous [2] work.

Turning now to 1,3-disubstituted cyclopentanes, the most notorious example is that of 1,3-dimethylcyclopentanes (the early erroneous stereochemical assignments had to be reversed after stereospecific synthesis [8]) for which thermochemical measurements led to $\Delta G°$ 0.5 kcal mol^{-1} in favour of the *cis*-isomer [4,9] with $\Delta H°$ 0.54 kcal mol^{-1} and $\Delta S°$ *ca.* 0 (gas phase; 298—600 K).[4,9,†] However, palladium-[5b] or aluminum bromide-catalysed[5c] equilibration of 1,3-dimethylcyclopentanes (and other dialkyl derivatives [5b]) led to nearly equal proportions of the *cis*- and *trans*-isomers. This discrepancy is still unexplained and could perhaps be due to phase effects.

For the *cis* ⇌ *trans* equilibrium of 3-substituted cyclopentanols, aluminum isopropoxide equilibration gave $\Delta G°_{298}$ −0.05 and −0.2 kcal mol^{-1} for the t-butyl [12] and methyl [13] derivatives respectively.

Finally, the diastereoisomeric cyclopentane-1,3-dicarboxylic acids were equilibrated in boiling 20% aqueous hydrochloric acid to a 1 : 1 *cis–trans* mixture, *i.e.* K *ca.* 1.[14]

All these results are in line with the general phenomenon that epimeric 1,3-disubstituted compounds exhibit surprisingly similar physical properties to the extent that they are almost inseparable from their mixtures.[1,12] This led to the inference that the high conformational mobility of the cyclopentane ring due to its albeit inhibited pseudorotation causes a levelling off in the physical properties of the stereoisomers. A final proof however had still to be put forward.

The most notable result in the present work is the practically zero enthalpy difference in the whole series. That this is indeed a ring effect is supported by the analogous behaviour of the stereoisomeric cyclopentane-1,3-dicarbonitriles *cis* ⇌ *trans* equilibrium in Bu^{t}OH–Bu^{t}OK ($\Delta G°_{322}$ 0.08 ± 0.01, $\Delta H°$ 0.00 ± 0.03 kcal mol^{-1}, $\Delta S°$ 0.2 ± 0.1 cal mol^{-1} K^{-1}).

We think that this provides *direct* proof for the lack of steric interactions between 1,3-substituents on the five-membered ring, *i.e.* whenever possible, the high flexibility of the latter enables 1,3-substituents to move away from one another so as to minimize interactions. The practical conformation meaning of this statement is, unlike in cyclohexane, the complete absence of the notion of conformational energies (*i.e.*, *A* values [3a]) of substituents in cyclopentanes, since the five-membered ring adjusts itself to the substituent requirements and not *vice versa*.[3] Any extrapolation, therefore, of cyclohexane conformational analysis to cyclopentane behaviour is necessarily unwarranted and can lead to erroneous conclusions. We shall elaborate further on this point in a forthcoming publication.[2,15]

Turning now to the entropy term, our approach in this work was designed in an attempt to assert its origin. The working hypothesis was based on the consideration that the *cis*-Me_2 and *cis*-Et_2 diesters are *meso*-compounds whereas their *trans*-isomers are racemic mixtures. This could result in an entropy of mixing contribution of $R\ln 2$ in favour of the latter. On the other hand, both *cis*- and *trans*-MeEt diesters occur as racemic mixtures and therefore no entropy difference stemming from mixing terms should be obtained. Actually, the argument is somewhat more complex and, at this point, reference to the situation in cyclohexane is in order.

Allinger and Curby [16] had determined the relative stabilities of dimethyl and diethyl cyclohexane-1,3-dicarboxylate and calculated thereof the *cis* ⇌ *trans* free energy difference $\Delta G°_{340}$ as 0.58 kcal mol^{-1}. Reasoning that the racemic *trans*-isomer should exhibit an

* 1 cal = 4.18 J.

† It is noteworthy that, heavily drawing from cyclohexane conformational analysis, Haresnape [8b] hypothesised that the fact that *cis*-1,3-dimethylcyclopentane is more stable than its *trans*-isomer should be due to its occurrence as a 1,3-diequatorial envelope form. Subsequently, force field calculations [10,11] showed that this is not necessarily so and a number of other forms (mainly half-chairs) are of lower energy and hence should, at least in part, be populated.[3c]

[4] (*a*) M. B. Epstein, G. M. Barrow, K. S. Pitzer, and F. D. Rossini, *J. Res. Nat. Bur. Stand.*, 1949, **43**, 245; (*b*) A. L. Liberman, O. V. Bragin, G. K. Gur'yanova, and B. A. Kazanskii, *Doklady Chem.*, 1963, **148**, 70.

[5] O. A. Aref'ev, V. A. Zakharenko, and A. A. Petrov, (*a*) *Neftekhimiya*, 1964, **4**, 854 (*Chem. Abs.*, 1965, **62**, 8967d); (*b*) 1966, **6**, 505 (*Chem. Abs.*, 1966, **65**, 16835e); (*c*) V. A. Zakharenko, I. O. Delone, and A. A. Petrov, *ibid.*, 1968, **8**, 675 (*Chem. Abs.*, 1969, **70**, 37029n).

[6] (*a*) G. L. Fonken and S. Shiengthong, *J. Org. Chem.*, 1963, **28**, 3485; (*b*) D. S. Seigler and J. J. Bloomfield, *ibid.*, 1973, **38**, 1375.

[7] D. Y. Curtin, H. Gruen, Y. G. Hendrickson, and H. E. Knipmeyer, *J. Amer. Chem. Soc.*, 1961, **83**, 4838.

[8] (*a*) S. F. Birch and R. A. Dean, *J. Chem. Soc.*, 1953, 2477 and references cited therein; (*b*) J. N. Haresnape, *Chem. and Ind.*, 1953, 1091.

[9] F. D. Rossini, K. S. Pitzer, A. L. Arnett, R. M. Brown, and G. C. Pimental, ' Selected Values of Physical and Thermodynamic Properties of the Hydrocarbons and Related Compounds,' Carnegie Press, Pittsburgh, 1953, p. 711.

[10] N. L. Allinger, M. A. Miller, E. A. van Catledge, and J. A. Hirsch, *J. Amer. Chem. Soc.*, 1967, **89**, 4345.

[11] R. C. Lugar, Ph.D. Dissertation, University of Pennsylvania, 1969.

[12] J. C. Richer and C. Gilardeau, *Canad. J. Chem.*, 1965, **43**, 3419.

[13] R. G. Haber and B. Fuchs, *Tetrahedron Letters*, 1966, 1447.

[14] S. C. Temin and M. E. Baum, *Canad. J. Chem.*, 1965, **43**, 705.

[15] B. Fuchs and P. S. Wechsler, *Tetrahedron*, in the press.

[16] N. L. Allinger and R. J. Curby, jun., *J. Org. Chem.*, 1961, **26**, 933.

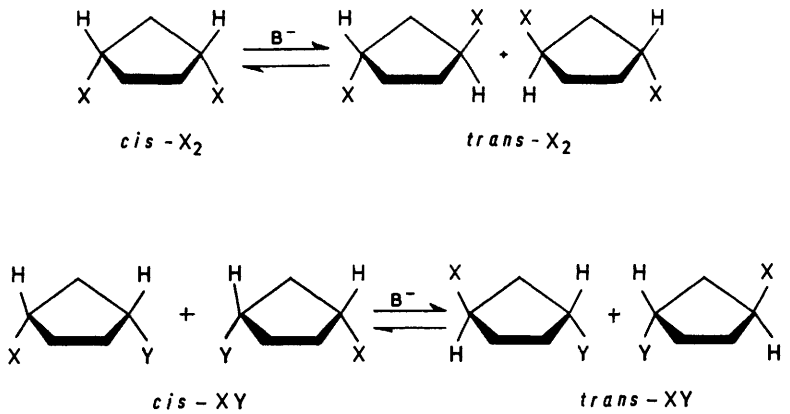
increased entropy by $R\ln 2$ over the *meso-cis*-isomer, these authors calculated $\Delta H°$ 1.05 kcal mol^{-1}, which they took as a measure for the conformational energy of the methoxycarbonyl group.[16] Robinson and his co-workers [17] have reopened and elaborated the investigation in a temperature dependent study of the dimethyl cyclohexane-1,3-dicarboxylates, reporting $\Delta G°_{336}$ 0.7, $\Delta H°$ 1.06 $\pm$ 0.06 kcal mol^{-1}, and $\Delta S°$ 0.95 $\pm$ 0.3 cal mol^{-1} K^{-1}. To resolve the discrepancy in the free energy values we have rechecked the measurements and found the latter value to be correct. There remains the question of the entropy. Obviously, the original assumption [16] of an $R\ln 2$ entropy of mixing was, at least in part, not supported by experiment and shows the pitfalls in such treatments. Robinson *et al.*[17] have tentatively attributed this decrease in the entropy term to a restricted rotational freedom for the axial ester group in the *trans*-species although no similar effect was apparent for isopropyl esters.[17]

Be this as it may, the main difference between the six- and the five-membered 1,3-disubstituted compounds lies in that while the *cis*-cyclohexane derivatives are virtually fixed in one, diequatorial form the analogous cyclopentane derivatives are relatively free to assume a large variety of ring conformations. This is supported by the zero enthalpy as well as by comparison with related systems.[15]

In our equilibria (1a), (2a), (1b), (2b), (3d), and (3e), *i.e.*, *cis*-Me_2 $\rightleftharpoons$ *trans*-Me_2 and *cis*-Et_2 $\rightleftharpoons$ *trans*-Et_2 one has to account for the 0.7—1.0 cal mol^{-1} K^{-1} entropy differences as compared to the expected value of 1.38 cal mol^{-1} K^{-1} ($R\ln 2$). One might be tempted to invoke two effects (*cf.* Scheme 2). One is the possible contribution of C_2 symmetrical conformations in the *trans*-isomers (double quasiequatorially substituted half-chairs [3]) which would introduce entropy of symmetry terms for these isomers thus reducing the entropy difference. At the same time, the symmetrically substituted *cis*-isomers do not necessarily exhibit C_s symmetry due to the pseudorotational mobility discussed above, which could cause an increase in their entropy by mixing terms. However, in the MeEt case neither argument applies because of the lack of any symmetry imposed by the different substituents, and yet a similar (1 cal mol^{-1} K^{-1}) entropy difference was found.

We must conclude, therefore, that this positive entropy term is inherent to the cyclopentane system under study and apparently originates in the more variegated conformational population of the *trans*-isomers due to a less restricted pseudorotation. This is fully supported by energy calculations and n.m.r. spectroscopic analysis in a series of related 1,3-dihalogeno- and dicyano-cyclopentanes.[15]

The experimental entropy differences of transesterification reactions (3a and b) (Table 1) approach the value of $2R\ln 0.5 = 2.74$ cal mol^{-1} K^{-1}. This is, actually,



SCHEME 2 Epimerization (*cis* $\rightleftharpoons$ *trans*) equilibria of dimethyl, diethyl (X_2), and methyl ethyl (XY) esters of the cyclopentane-1,3-dicarboxylic acids

in accord with statistical requirements. Following the substitution patterns (XY *versus* XX + YY) the reactants are twice as probable as the products and $\Delta S° = R\ln(p_2/p_1)$ (p = probability). However, additional small entropy factors in these reactions might operate.

EXPERIMENTAL

General.—N.m.r. spectra were recorded (in $CDCl_3$ and/or CCl_4) on 100 MHz Varian and, when indicated, on 60 MHz JEOL C-60 HL spectrometers. I.r. spectra were recorded on a Perkin-Elmer 337 instrument. Mass spectra were recorded on a Du Pont 21-491 B instrument. G.l.c. was performed on Varian Aerograph (VA) model 90-P and on VA series 1800 gas chromatographs (columns: SAIB 18% on Chromosorb W and DEGA 10% on Chromosorb W).

cis-Cyclopentane-1,3-dicarboxylic acid (norcamphoric acid) was prepared by ozonolysis of norbornene according to Perry,[18] with slight modifications.

cis-*Cyclopentane-1,3-dicarboxylic Acid Anhydride* (*Norcamphoric Anhydride*).—Norcamphoric acid (25 g) and distilled acetic anhydride (30 ml) were gently refluxed (moisture guard tube) for *ca.* 1 h. Norcamphoric anhydride separated upon cooling. It was recrystallized (18—20 g) from benzene (decolourizing charcoal), m.p. 163—164°

[17] B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, 1964, **20**, 747.
[18] R. H. Perry, jun., *J. Org. Chem.*, 1959, **24**, 829.

(lit.,[19,20] 163—164°). The dimethyl and diethyl esters of the norcamphoric acid were obtained by esterification with the respective alcohol. All the esters were purified by distillation at 25—30 Torr (Table 2), n.m.r., dimethyl esters, *cis*, δ 3.50 (6 H, s, ester CH_3); *trans*, δ 3.60 (6 H, s, ester CH_3); diethyl esters: *cis* and *trans*, δ 1.23 (6 H, t, *J* 7 Hz, ester CH_3) and 4.05 (4 H, q, *J* 7 Hz, ester CH_2), $\nu_{max.}$ 1 740 cm^{-1} (C=O, all esters).

Ethyl Methyl cis-*Cyclopentane*-1,3-*dicarboxylate* (*Ethyl Methyl Norcamphorate*).—Norcamphoric anhydride (15 g) was suspended in absolute ethanol (150—200 ml). An ethanol solution (50 ml) containing 1 equiv. of sodium ethoxide was added dropwise and under stirring (moisture guard tube); the solvent was removed *in vacuo* and replaced by water (100 ml). The aqueous solution was extracted with a little methylene chloride and then acidified with hydrochloric acid down to pH 2. The acidic solution was extracted with methylene chloride. The resulting organic solution was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The residue, consisting of crude *cis*-monoethyl norcamphorate (90%) was distilled, b.p. 136—137° at 0.2 Torr, δ 1.25 (3 H, t, *J* 7 Hz, ester CH_3), 4.12 (2 H, q, *J* 7 Hz, ester CH_2), and 8.50br (s, acidic H), $\nu_{max.}$ 3 000br (OH) and 1 720br cm^{-1} (C=O).

The monoethyl ester obtained in this way was esterified with diazomethane. The resulting *ester* was purified by distillation, b.p. 143° at 25 Torr. G.l.c. analysis revealed total configurational purity, δ 1.25 (3 H, t, *J* 7 Hz, ethyl ester CH_3), 3.60 (3 H, s, methyl ester CH_3), and 4.06 (q, *J* 7 Hz, ethyl ester CH_2), $\nu_{max.}$ 1 750 cm^{-1} (C=O), *m/e* 200 (M^+) (Found: C, 60.0; H, 8.2. $C_{10}H_{16}O_4$ requires C, 59.95; H, 8.2%).

Ethyl Methyl trans-*Cyclopentane*-1,3-*dicarboxylate* (*Ethyl Methyl Isonorcamphorate*).—*trans*-Cyclopentane-1,3-dicarboxylic acid (95% configurational purity; 5 g) was dissolved in water (30 ml). 1 Equiv. of sodium hydroxide, dissolved in the same volume, was added dropwise and under stirring. The solvent was then removed *in vacuo* and the crude monosodium dicarboxylate stirred with methanol (25 ml). The resulting suspension was esterified with diazomethane. The solvent was removed and replaced by water (150 ml); the almost neutral aqueous solution was extracted with methylene chloride; the resulting organic phase was found to contain dimethyl ester (*ca.* 1.5 g; *ca.* 95% *trans*). The aqueous solution was acidified down to pH and extracted with methylene chloride; the solution was dried ($MgSO_4$) and the solvent removed *in vacuo*; the residue was distilled at 128° and 0.2 Torr; the product was monomethyl isonorcamphorate (configurational purity *ca.* 95%), δ 3.60 (3 H, s, ester CH_3) and 9.0br (s, acidic H). The monomethyl ester was ethylated with 1-ethyl-3-*p*-tolyltriazene.[21] The resulting ethyl methyl ester (*ca.* 95% *trans*) was distilled at 135° and 25 Torr. It was further purified by preparative g.l.c. (170°; SAIB column), δ 1.24 (3 H, t, *J* 7 Hz, ethyl ester CH_3), 3.60 (3 H, s, methyl ester CH_3), and 4.05 (2 H, q, *J* 7 Hz, ethyl ester CH_2), $\nu_{max.}$ 1 750 cm^{-1} (C=O), *m/e* 200 (M^+) (Found: C, 59.95; H, 8.2%).

cis- *and* trans-*Cyclopentane*-1,3-*dicarbonitrile*.—Norcamphoric acid (16 g) was mixed with urea (10 g) in a round-bottomed flask (25 ml) fitted with a cold finger sublimator. The mixture was heated gradually (oil-bath) to 160° at atmospheric pressure and the melt was stirred for 3 h. A sublimate (*ca.* 4 g) was collected, m.p. 118°. The residue was crystallized and recrystallized from ethanol giving norcamphoramide (5 g), m.p. 224° (lit.,[21] 224—226°), $\nu_{max.}$ (KBr) 3 360 (s, sharp), 3 310 (shoulder), and 3 160 (s, sharp) (N–H), and 1 660 (s, sharp) and 1 630 cm^{-1} (s, sharp) (C=O), δ (60 MHz; D_2O) 2.15br (6 H, unresolved m) and 3.05 (2 H, unresolved m). The diamide was boiled under reflux (moisture guard tube) with thionyl chloride (20 ml) for 3 h. Excess of reagent was distilled off; the residue was taken up in methylene chloride and shaken with 5% aqueous sodium carbonate; the solution was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The residue was purified by chromatography on basic alumina with chloroform as eluant; the first 200 ml of eluate contained 3.5 g of a liquid which by g.l.c. analysis contained two components in a *ca.* 2 : 5 ratio. They were separated by preparative g.l.c. (DEGA column; 200°) and further purified by distillation.

The trans-*epimer* (shorter retention time on g.l.c.) had b.p. 178° at 25 mmHg, $\nu_{max.}$ 2 230 cm^{-1} (m to s, sharp) (C≡N), *m/e* 120 (M^+) (Found: C, 69.95; H, 6.85. $C_7H_8N_2$ requires C, 69.95; H, 6.7%). The cis-*epimer* (longer retention time) had b.p. 178° at 25 mmHg, $\nu_{max.}$ 2 230 cm^{-1} (m to s, sharp) (C≡N), *m/e* 120 (M^+) (Found: C, 69.12; H, 6.7%).

Equilibrium Experiments.—A 250 ml Quickfit wide-neck reactor with five-socket flat flange lid was equipped with a hot plate–magnetic stirrer, oil-bath, double surface reflux condenser (or, alternatively, connections to a thermostatted bath with circulation system), and a normal Wertheim thermometer (0.1 °C graduation). Three especially adapted test tubes, each carrying a magnet and a silicone rubber septum stopper were introduced in three of the ground glass necks. Analytical grade solvent (75 ml) was introduced into the reactor (or, alternatively, this was connected to the thermostatted bath) and brought to gentle reflux, providing a constant temperature. Substrate (100 mg) was placed in each test tube and this was flushed with deoxygenated (Fieser solution) dry nitrogen gas for 5 min (by means of two hypodermic needles penetrating the septum, one being connected to the nitrogen source); at the end of the flushing, the exit needle was removed, and the entry needle immediately thereafter. A certain amount of alkoxide solution (stock kept under nitrogen atmosphere and previously titrated), calculated to provide the required substrate and catalyst concentrations was introduced by means of a hypodermic syringe, with magnetic stirring. This was continued for all the equilibration period. At the end of this, titrated alcoholic (in methanol and ethanol, according to the case; when the reaction took place in t-butyl alcohol, the solvent of the acidic solution was isopropyl alcohol) hydrochloric acid solution (1—2 ml; 10—20% excess over the stoicheiometric amount) was preheated to the temperature of the experiment and, by means of an equally preheated syringe equipped with a long (13 cm) needle, was instantaneously injected into the bulk of the reaction mixture. The test tube was immediately immersed in an ice–salt bath for 2 min and cold (0—10°) distilled water (3—4 ml) were added; the mixture was saturated with solid sodium chloride and extracted with dichloromethane. The organic solution was shaken with 5% sodium hydrogen carbonate (1—2 ml); the extractions were carried on in test tubes equipped with rubber septum

[19] P. C. Guha and K. S. Ranganathan, *Ber.*, 1936, **69**, 1199 and papers cited therein.

[20] K. T. Popischill, *Ber.*, 1898, **31**, 1950.

[21] E. H. White, A. A. Baum, and D. E. Eitel, *Org. Synth.*, 1968, **48**, 102.

stoppers. The organic solution was dried over 4 Å molecular sieve, filtered, and the solvent distilled. The residue was dissolved in chloroform (0.5 ml) and analysed by g.l.c.

Blank tests were done at the highest working temperatures in each series with pure stereoisomers and with especially prepared epimeric mixtures, using solutions of catalyst that were previously neutralized with proportional amounts of acidic solution. They insured that no epimerization (or transesterification) took place during the acidic quenching and the work-up. Ester recovery from equilibrium experiments were determined separately; analysis was performed gravimetrically and/or by the use of an internal standard (ethyl phenylacetate) in g.l.c.; the extent of recovery was 70—100%.

The dimethyl and the diethyl norcamphorates and isonorcamphorates were separated on the SAIB column at 170°, the dinitriles on DEGA at 190°, and the dimethyl camphorates and isocamphorates on DEGA at 160°. The SAIB column was also used in the resolution of mixtures where all the six methyl and ethyl esters of norcamphoric and isonorcamphoric acids were present. A sample separation is shown in Figure 4. The areas under the peaks in g.l.c. analysis were measured by means of a disc integrator or by means of a planimeter. Calibration curves of molar ratios *versus* area ratios of standard mixtures of pure samples of the equilibrating substances were prepared. The resulting conversion factors in the case of epimeric compounds were practically unity.

Constructive remarks by Professor E. L. Eliel and Dr. M. J. T. Robinson are greatly appreciated.

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