and VIa (1.5 g). The mixture obtained in this manner was further purified by dry column chromatography using a loading ratio of 100:1. The column was run, using 500-mg samples of the mixture. A portion of compounds VIa and Va isolated by the above technique was then purified by tlc on silica gel (0.5-mm plate thickness) to obtain samples for spectra. Both epimers were amorphous solids that precipitated from ether:petroleum ether: mp Va 101–104° and VIa 92–96°. Va: ir (KBr) λ_{max} 3350 (broad), 1640, 1620, 1505, 1460, 1165, 1100, 950, 905, 790 cm^{-1}; nmr ($CDCl_3$) δ 6.4–6.7 (2 H, arom), 4.9–5.7 (m, 4 H, on addition of D_2O one peak disappears), 4.32 (s, 1 H), 1.27 (s, 3 H). VIa: ir (KBr) λ_{max} 3400 (broad), 1645, 1620, 1505, 1460, 1149, 1097, 940, 802 cm^{-1}; nmr ($CDCl_3$) δ 6.3–6.6 (2 H, arom), 4.9–5.7 (m, 4 H, on addition of D_2O one peak disappears), 4.36 (s, 1 H), 1.38 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynorisomorphine 3-Acetate (VIb).** Compound VIa (8 mg, 0.023 mmol) was dissolved in pyridine (1 ml) and acetic anhydride (4 μl, 0.04 mmol) was added. The solution was allowed to stand overnight at room temperature after which time the solvent was evaporated *in vacuo*. Thin-layer chromatography showed only one compound present in the residue. An ir spectrum (KBr) of the oil showed an absorption at 1770 cm^{-1} corresponding to the 3-acetate group; nmr ($CDCl_3$) δ 6.5–6.8 (2 H, arom), 5.9 (broad, 1 H, disappears on addition of D_2O), 5.0–5.6 (m, 3 H), 4.34 (s, 1 H), 2.29 (s, 3 H), 1.23 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine 3-Acetate (Vc).** Acetylation of Va (25 mg) was carried out as for VIb. An ir spectrum of the oil obtained verified the presence of the 3-OAc (1775 cm^{-1}); nmr ($CDCl_3$) δ 6.5–6.8 (2 H, arom), 4.9–5.4 (m, 3 H), 4.35 (s, 1 H), 3.88 (broad, disappears on addition of D_2O) 3.39 (broad, disappears on addition of D_2O), 2.31 (s, 3 H), 1.30 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynorisomorphine 3,14-Diacetate (VIc).** Compound VIa (14 mg) was dissolved in a minimum amount of acetic anhydride and heated under reflux for 30 min. The solvent was removed *in vacuo* to give 15 mg of VIc as an oil. An ir spectrum (KBr) showed peaks at 1770 and 1735 cm^{-1} corresponding to the 3- and 14-acetate groups, respectively; nmr ($CDCl_3$) δ 6.4–6.7 (2 H, arom), 4.9–5.7 (m, 4 H, one peak disappears on addition of D_2O), 4.38 (s, 1 H), 4.35 (H^9, superimposed on H^5), 2.31 (s, 3 H), 2.15 (s, 3 H), 1.21 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine 14-Acetate (Vb).** Compound Va, isolated from the reaction of naloxone 3,14-diacetate with methyllithium, was purified by tlc on silica gel using the system previously described to give Vb. An ir spectrum (KBr) contained a carbonyl absorption at 1745 cm^{-1}. The oil could not be induced to crystallize; nmr ($CDCl_3$) δ 6.4–6.6 (2 H, arom), 4.9–5.6 (m, allyl group), 4.34 (s, 1 H), 4.18 (d, J = 6, 1 H), 2.06 (s, 3 H), 1.30 (s, 3 H).

Acknowledgment. This work was supported in part by the National Institutes of Mental Health, Grant MH 21365. We thank Mr. B. Cooley of Waters Associates for the HPLC separations.

Registry No.—IIa, 20410-95-1; IIb, 53154-12-4; III, 53154-13-5; IVa, 53154-14-6; IVb, 53154-15-7; IVc, 53154-16-8; IVd, 53154-17-9; Va, 53154-18-0; Vb, 53154-19-1; Vc, 53154-20-4; VIa, 53154-21-5; VIb, 53154-22-6; VIc, 53154-23-7; *p*-toluenesulfonyl chloride, 98-59-9; naloxone, 465-65-6; naloxone 3,14-diacetate, 50510-01-5.

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Stereochemistry of Nucleophilic Addition Reactions. The Addition of Diethyl Malonate to Ethyl 4-*tert*-Butylcyclohexene-1-carboxylate. Equilibration of 1-*tert*-Butyl-3-carboxymethylcyclohexane-4-carboxylic Acids

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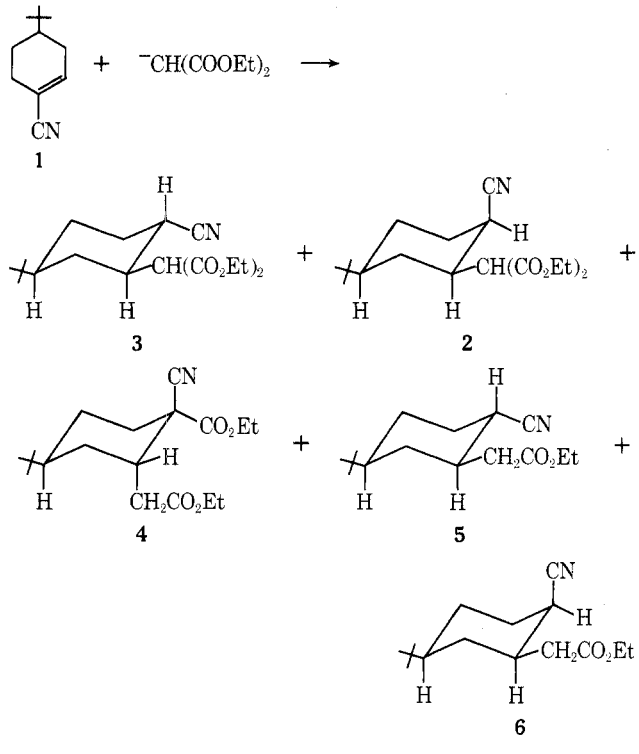
Received July 15, 1974

The Michael addition of diethyl malonate to ethyl 4-*tert*-butylcyclohexene-1-carboxylate gives three of the four possible malonate adducts and the corresponding acetates. The effect of solvent upon the stereochemistry of the addition has been investigated. Under conditions of kinetic control the main product is the *r*-1,*c*-3,*c*-4 isomer (**10**) while under thermodynamic control conditions the *r*-1,*c*-3,*t*-4 isomer predominates. No product of abnormal addition is observed. Equilibration of these adducts with base proceeds mainly by reversal and re-addition. The regioselectivity of the protonation of the intermediate anion is discussed in terms of current theories and the results reconcile the various theories. The equilibrations of the dicarboxylic acids **14**, **15**, **16** and **20** have been studied. $\Delta G°$ for **15** ⇌ **16** is smaller than expected, and for **14** ⇌ **20** less of the diaxial epimer is formed than would be predicted on the basis of $\Delta G°(CO_2H)$. Possible explanations are proposed for these observations.

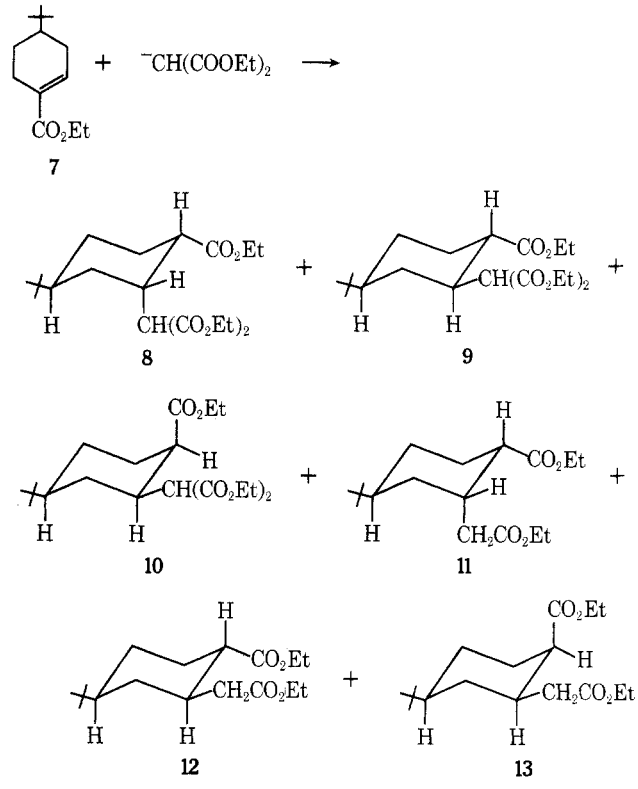
The stereochemistry of some nucleophilic additions to activated olefins of rigid conformation has been reported. Under conditions of kinetic control, the diethyl malonate anion in ethanol solution adds to 4-*tert*-butyl-1-cyanocyclohexene (**1**) to give the addition product with the malonate group equatorial and the cyanide group axial as the

main product (2), together with the (e)-malonate (e)-nitrile (3) as the minor product.[1] Under conditions of thermodynamic control, the latter was the main product. No axial malonate could be detected, but small amounts of the product of "abnormal" Michael addition, ethyl *r*-1-*tert*-butyl-*t*-3-carbethoxymethyl-*c*-4-cyano-*t*-4-cyclohexanecarboxylate (4), were obtained, which resulted from the rearrangement of the initially formed axial malonate anion intermediate. The two acetates, 5 and 6, were also obtained in a nonprotic solvent, but the main product was that of "abnormal" addition. On the other hand, the addition of thiophenoxide ion to the above unsaturated nitrile in ethanol gave both possible products containing an axial thiophenoxy group, the main product under both conditions of kinetic and thermodynamic control being the (a)-thiophenoxy-(e)-cyano conformer.[2] In tetrahydrofuran solution, some of the (e)-thiophenoxy-(a)-cyano conformer is also formed.



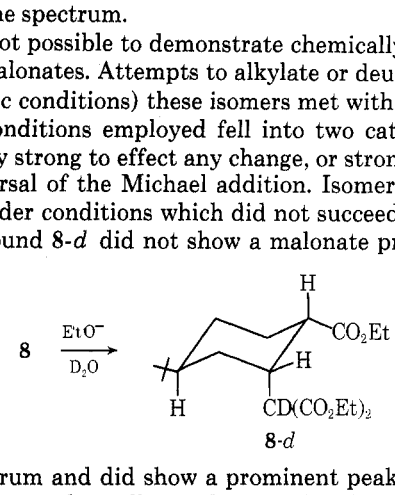
The preferred equatorial approach of the bulky malonate was attributed[1] to large diaxial nonbonded interactions in the transition state for axial addition, which transition state was assumed to resemble the intermediate. With smaller nucleophiles such as PhS^- and Cl^- such 1,3-diaxial repulsions would be much less important, and axial approach of the nucleophile would be favored because of almost continuous overlap between the developing σ bond and the conjugated system in the formation of the transition state leading to axial product.[2]

The question arose as to whether or not replacement of the relatively small, linear nitrile group by the relatively larger, nonlinear carbethoxy group would lead to the same results in the Michael addition. Ethyl 4-*tert*-butylcyclohexene-1-carboxylate (7) was readily synthesized by hydrolysis of the nitrile (1) with 40% sulfuric acid followed by esterification of the acid with ethanol and acid. Indeed, addition of diethyl malonate to the ester (7) proved not to be entirely analogous to the addition to the nitrile (1). Six products were identified: three malonates (8, 9, and 10) and the corresponding acetates (11, 12, and 13). Five of the six products were isolated by preparative gas chromatography (the sixth, 11, was present in insufficient quantities for isolation; it was identified by its synthesis from the known dicarboxylic acid and comparison of glc retention times). That 8, 9, and 10 were indeed malonates was demonstrated by nmr spectroscopy and mass spectrometry. The nmr spectrum of each isomer showed a distinctive malonate proton signal,[3] a very sharp doublet around δ 3.7, $J \simeq 12$ Hz [8, δ 3.65 (J = 12 Hz); 9, δ 3.70 (J = 13 Hz); 10, δ 3.76 (J = 11 Hz)].



The mass spectrum of each compound showed a strong peak at *m/e* 160. For 8 and 9 it is the base peak; for 10, it has a relative intensity of 67% and is the second most intense peak in the spectrum. Williams and coworkers[4] showed that monosubstituted malonic esters undergo the McLafferty rearrangement to give a peak due to $EtOOCH{=}C(OH)OEt \cdot^+$ at *m/e* 160 which is generally the base peak for the spectrum.

It was not possible to demonstrate chemically that 9 and 10 were malonates. Attempts to alkylate or deuterate (both under basic conditions) these isomers met with unqualified failure. Conditions employed fell into two categories: not sufficiently strong to effect any change, or strong enough to cause reversal of the Michael addition. Isomer 8 was deuterated under conditions which did not succeed with 9 and 10. Compound 8-*d* did not show a malonate proton in the nmr spectrum and did show a prominent peak at *m/e* 161 (84%) and a much smaller peak at 160 (28%).

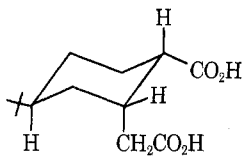


The configurations of 8, 9, and 10 were determined by conversion to known dicarboxylic acids, 14–16.[1] The acetates 11, 12, and 13 were synthesized by esterification of the corresponding dicarboxylic acids for comparison with material previously obtained from preparative gas chromatography. The acetates could also be synthesized by decarbethoxylation of the malonates in a sealed tube over 10%

Table I
Michael Additions in Ethanol and Toluene

Olefin	Solvent	T, °C	Base	Main product
Nitrile (1)	EtOH	R.T.	EtO^-	*r*-1, *c*-3, *c*-4 (2)
	EtOH	80	EtO^-	*r*-1, *c*-3, *t*-4 (3)
	toluene	110	Na	Abnormal prod (4)
Ester (7)	EtOH	R.T.	EtO^-	*r*-1, *c*-3, *c*-4 (10)
	EtOH	80	EtO^-	*r*-1, *c*-3, *t*-4 (9)
	toluene	110	Na	*r*-1, *c*-3, *c*-4 (9)

palladium on charcoal at elevated temperatures (10 + 10% Pd–C → 13 + 12). The reaction was complicated by the occurrence of equilibration as well as decarbethoxylation, but the latter reaction was faster, and if the reaction was run for an appropriately short time, virtually stereospecific decarbethoxylation could be observed.



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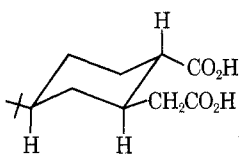

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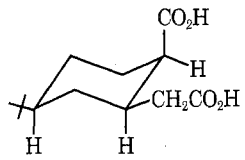

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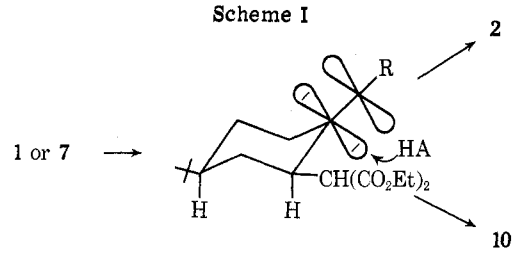
Solvent plays a major role in determining the stereochemistry of the addition of malonate anion to 1. The Michael addition to the ester (7) did not follow entirely the same pattern. The results are summarized in Table I. The reactions of the two olefins are entirely analogous under kinetic control conditions, *i.e.*, in ethanol at room temperature using sodium ethoxide as the base. Both olefins gave the *r*-1,*c*-3,*c*-4 isomer as the predominant product (Scheme I). Protonation occurs from the equatorial direc-

Scheme I



tion in both cases, despite the disparity in size of the nitrile and carboethoxy groups. Even with a bulky equatorial substituent at C-3, attack leading to equatorial proton is the "least hindered" giving the thermodynamically less stable product. The substituent at C-4 is axial, in complete accord with Zimmerman's theory[5] that protonation occurs preferentially from the least hindered (usually equatorial) side.

Under thermodynamic control conditions (sodium ethoxide–ethanol under reflux) both the nitrile (1) and the ester (7) give the thermodynamically more stable diequatorial products 3 and 9, respectively, again in accord with Zimmerman's theory.[5]

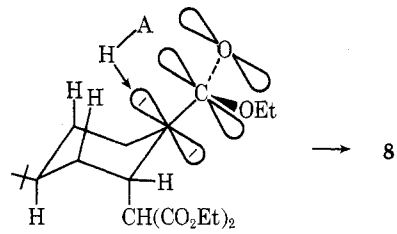
The reactions of the ester (7) and the nitrile (1) with diethyl sodiomalonate in aprotic solvent are not at all similar. In toluene or dioxane 1 gave mainly the rearranged product (4), while the ester (7) gave no detectable amount of a rearranged product, and the products of the Michael addition

Table II
Michael Addition to the Ester (7) in Various Solvents

Solvent	T, °C	Time, hr	Molar ratios of 8	9	10	Overall yield, %
Ethanol	R.T.	96		33	67	45
Ethanol	80	48	17	72	11	65
Toluene	110	48	1	39	60	25
Diethyl carbonate	Reflux	12	19	64	17	16

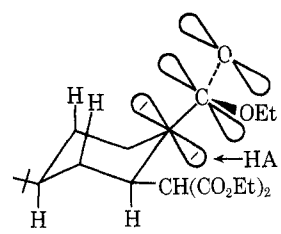
to the ester in aprotic solvents were the same as those in protic solvent, except that the product ratios changed and that higher temperatures were often needed to effect the addition; also the yields were relatively low. The results are summarized in Table II.

The formation of isomer 8 is the result of the less favored[1] axial addition of malonate to the olefin. With an axial substituent at C-3, the entering proton donor finds axial approach past the syn-diaxial hydrogens less hindered than equatorial approach. This result is in complete agreement with the views of Malhotra and Johnson[6] in the sense that in 17 an axial group (not, however, formed as a result of $A^{(1,3)}$ strain) is adjacent to the carbanionic center, and it would sterically hinder the approach of a proton from that side.



17

Thus, the results of one Michael addition seem to reconcile the views of Zimmerman,[5] Bordwell,[7] and Johnson.[6] When the malonate group at C-3 is equatorial, considerable $A^{(1,3)}$ strain undoubtedly exists in the intermediate 18, but this strain cannot be relieved by chair–chair interconversion, since the presence of the *tert*-butyl group at C-1 effectively freezes the conformation. Despite the $A^{(1,3)}$ strain, then, protonation occurs from the equatorial direction (18), which is still the least hindered direction, in accord with Zimmerman's theory. When the malonate is in an axial configuration, protonation occurs from the axial direction (17) which is now the least hindered. Aspects of the argument used by Bordwell will be discussed in a future paper. Suffice it to say here that the bending away of the vicinal groups in 18 would force the malonate moiety at C-3 up and block approach from the axial direction.



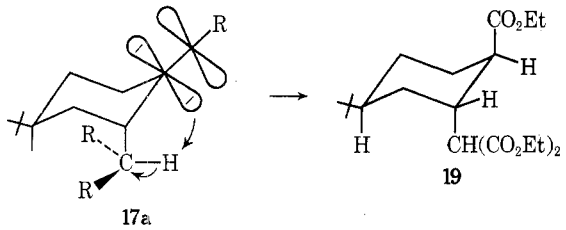
18

The question remains as to why no rearranged product is formed in the addition of diethyl malonate to the ester (7). One possible explanation is that the malonate groups at C-3 is in a configuration that sterically prohibits the necessary intramolecular attack (*vide infra*). Alternate explanations can be found in the literature. There are no examples

Table III
Equilibrations of the Dicarboxylic Acids

Compd	Catalyst	T, °C	K_{eq}	ΔG°, kcal/mol ± 0.01	ΔH°, kcal/mol	ΔS°, eu	ΔG°_{25}, kcal/mol
15	12 *N* HCl	240	0.89	+0.11			
15	10% Pd–C	240	0.97	+0.03			
15	5% NaOH	240	2.3	−0.84			
15 or 16	None	153	1.05	−0.04			
15 or 16	None	203	0.95	+0.05			
15 or 16	None	252	0.87	+0.135	−0.84 ± 0.06	−1.9 ± 0.3	−0.2 ± 0.1
14	12 *N* HCl	178	11.5	−2.18			
14	12 *N* HCl	198	9.0	−2.05			
14	12 *N* HCl	217	7.7	−1.98	−4.4 ± 0.1	−4.8 ± 0.1	−2.9 ± 0.2
14	12 *N* HCl	240	8.1	−2.13			
14	10% Pd–C	240	10.2	−2.28			
14	5% NaOH	240	49	−3.88			
12 or 13	10% Pd–C	249	4.88	−1.6			

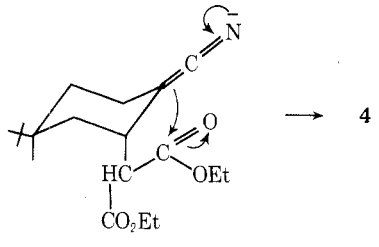
of an abnormal Michael addition occurring in the addition of diethyl malonate to an α,β-unsaturated ester, although many such reactions are known when diethyl methylmalonate is the Michael donor.[8] Several theories have been proposed to explain this observation. One is that the greater acid strength of the abnormal products is the driving force for the rearrangement. When diethyl malonate is the donor, both normal and abnormal products would have the same acidity, and hence no driving force for migration would be present.[9] Another possible explanation suggested that the malonate proton migrates more readily than the carbethoxyl group. When a C-monosubstituted malonate is the Michael donor a carbethoxyl group migrates more readily than an alkyl group.[10] This cannot apply to our reactions, since proton migration from the malonate moiety would lead to **19**, which is not observed. Furthermore, it is



17a 19

highly unlikely that the malonate would be in a rotational conformation that would permit such an intramolecular proton migration, since such a conformation would be one in which at least one of the carbethoxyl groups would have to be oriented under the cyclohexane ring (**17a**), which would be unstable relative to that rotational conformation in which the malonate hydrogen atom protrudes under the cyclohexane ring.

A more plausible explanation in the present case would consider the steric requirements of the transition state involved in the rearrangement process. Abramovitch and Struble[1] have supported the Holden–Lapworth mechanism, which requires a cyclobutanone-type transition state.

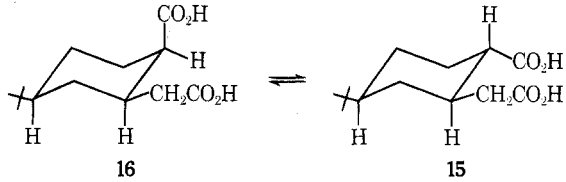


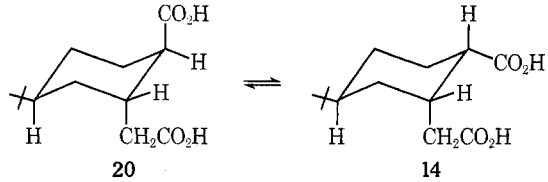
The steric requirements for this transition state may be rigid so that in the case of **17** the cyclobutanone ring cannot form. Thus, it is conceivable that steric interaction between the carbethoxyl group and the C-3 equatorial proton [*i.e.*, $A^{(1,3)}$ strain] causes some ring deformation that precludes formation of the cyclobutanone transition state.

Equilibrations of the malonates **8**, **9**, and **10** under thermodynamic control conditions should lead to a mixture of the epimeric malonates, *e.g.*, **9** ⇌ **10**, **8** ⇌ **19**. Equilibration of either **9** or **10** gave a mixture of all three malonate adducts, in the ratio expected for thermodynamic control conditions: **8:9:10 = 6:78:16**. Quantities of the olefin (**7**) were also present in the reaction mixture after equilibration. This, together with the formation of some of the axial adduct (**8**), suggests that reversal and subsequent readdition may well be an important reaction path (the product of axial addition could only arise this way), and that an actual equilibration of **9** and **10** *via* the C_4 carbanion could be only a minor pathway.

Attempted equilibration of **8** under thermodynamic control conditions gave unchanged **8**, *i.e.*, neither reversal nor equilibration occurred. This could be accounted for if the malonate proton is more acidic and/or more accessible than the proton at C-4. This is supported by the observation that **8** is the only one of the three malonates in which H–D exchange of the malonic ester proton was possible (*vide supra*).

Equilibration of the *r*-1-*tert*-Butyl-3-carboxymethylcyclohexane-4-carboxylic acids. The equilibrations of the dicarboxylic acids **14**, **15**, and **16** with 12 *N* hydrochloric acid, 5% sodium hydroxide, or 10% palladium on charcoal have been studied. The results are summarized in Table III.





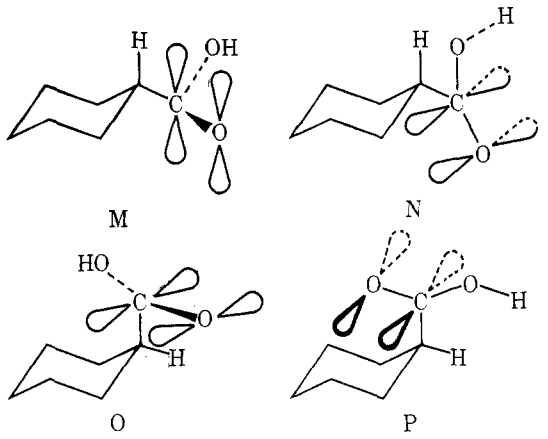


Figure 1. Cyclohexyl carboxyl group conformations.

The normal $\Delta G°$ value for a carboxyl group is in the range −1.15 to −1.6 kcal/mol at 25°,[11] and indeed we confirmed a value of $\Delta G°$ = −1.56 kcal/mol for 4-*tert*-butylcyclohexanecarboxylic acid at 258° (*cf.* $\Delta G°_{25}$ = −1.4 ± 0.1 kcal/mol, $\Delta H°$ = −1.63 ± 0.05 kcal/mol, and $\Delta S°$ = −0.8 eu[12]). Tichý and Sicher[13] reported $\Delta G°$ = −1.89 for the carboxylate anion at 180°, while Eliel[12] reported a preferred $\Delta G°_{25}$ value of −2.2 kcal/mol.

The equilibrium of **15** ⇌ **16** has a $\Delta G°$ much *smaller* than the normal value for the carboxyl group (−0.2 *vs. ca.* −1.4 kcal/mol at 25°). At 25° the equatorial isomer is very slightly favored, and at higher temperatures there is actually a preference for the axial epimer.

Tichý and Sicher[13] found a *larger* than normal $\Delta G°$ for the equilibrium of the *r*-1-*tert*-butyl-*c*-3-methyl-4-cyclohexanecarboxylate ion ($\Delta G°$ = −3.5 kcal/mol at 180°). They ascribed this to a steric effect of the methyl group preventing the axial COO^- from achieving its preferred rotational conformation (see Figure 1). They suggested that the preferred rotational conformation for an equatorial carboxyl was the "perpendicular" one (*e.g.*, N, Figure 1), while the preferred rotational conformation for the axial carboxyl was the "tangential" one (*e.g.*, O, Figure 1). pK_a data supported this assignment. van Bekkum, Verkade, and Wepster[14] concurred with this view, while Dunitz and Strickler[15] disagreed. The latter determined the structure of *trans*-1,4-cyclohexanedicarboxylic acid by X-ray analysis and found that the equatorial carboxyls prefer the rotational conformation in which they are syn planar with the ring, *i.e.*, M, Figure 1. Calculations indicated that an axial carboxyl would also prefer the syn-planar configuration, *i.e.*, O, Figure 1. They believed that it was unlikely that the same conformational requirements would hold for the more symmetrical carboxylate anion.

The major difference between our systems, and that of Tichý and Sicher is that ours involves the vicinal interaction of two polar groups (carboxyl and carboxymethyl and the corresponding anions) while theirs involves the interaction of a polar and a nonpolar group (carboxylate and methyl). Since their results are in the opposite direction to ours, one might conclude that polar interactions are very important in the free dicarboxylic acids and the dicarboxylate anions. The methyl esters **12** and **13**, on the other hand, behave normally when equilibrated at 249° with 10% palladium on charcoal ($-\Delta G°$ = −1.6 kcal/mol at 249°, compared with a literature[11] value of −1.1 kcal/mol at 25°) see (see Table III).

The results of the equilibrations **15** ⇌ **16** (Table III) indicate that for both the free acids *and* the carboxylate anion the axial epimer is stabilized more than usual relative to the equatorial epimer (or the equatorial isomer is unusually destabilized). Solvation may be ruled out as an important factor in the free acid equilibrations, since the same values are obtained whether or not the equilibration is carried out in a solvent and $\Delta S°$ is relatively small and negative (−1.9 eu). If solvation were important, a positive $\Delta S°$ would have been expected, assuming the more stable isomer were more highly solvated than the less stable one. This would be expected for an equatorial substituent since it is less hindered than an axial one. Solvation may play some role in the carboxylate anion equilibrations. Evaluation of this possibility is prevented by lack of data on equilibrations at various temperatures. Intramolecular hydrogen bonding may play a role in stabilizing **16** relative to **15**, but this effect cannot obtain in the dicarboxylate anion. In the latter case dipolar repulsion between the two carboxylate functions, as well as solvation, may be important.

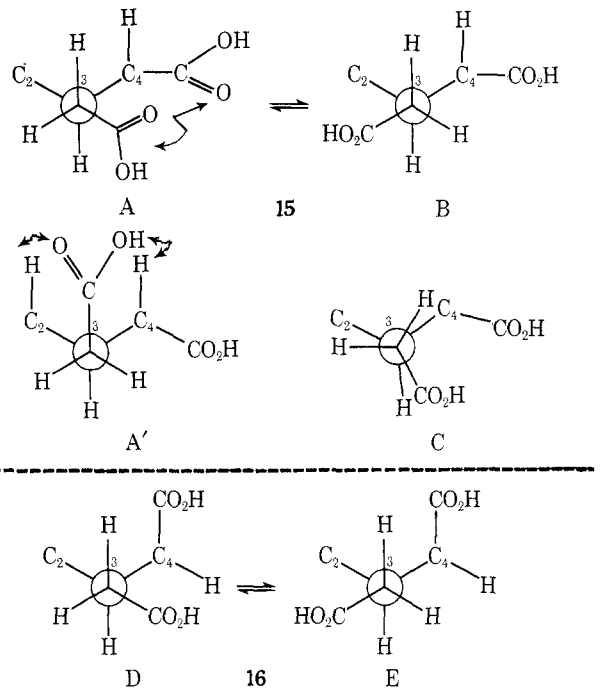


Figure 2. Rotational conformations of the carboxymethylene group in **15** and **16**.

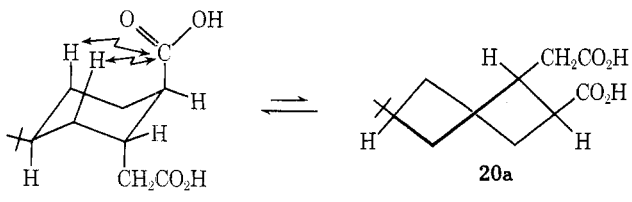
The results of the dicarboxylic acid equilibrations may perhaps be explained by a consideration of the possible rotational conformations available to the carboxymethyl group. In Figure 2, Newman projections are shown looking down the C-3-carboxymethylene bond, assuming (probably incorrectly) a perfect chair conformation for the cyclohexane ring. The expected ring flattering should, if anything, accentuate the arguments.

In **15** there are two possible reasonable staggered rotational conformations of the carboxymethylene group, *i.e.*, A and B (Figure 2). In A there would be considerable dipolar and steric interaction between the two eclipsed carboxyl groups [an $A^{(1,4)}$ interaction]. Consequently, **15** will prefer the conformation B. A certain percentage may exist in the eclipsed conformation C, but this would be energetically less favored than B, as would A′, which would essentially have an exocyclic axial carboxyl group.

The epimeric dicarboxylic acid, **16**, does not have the same conformational problems as does **15**, as far as the exocyclic carboxyl is concerned. There will be no steric or dipolar interactions between the carboxyl groups in either rotamer D or E. Hence, two approximately energetically equal rotational conformations are available to **16**, while only one is available to **15**. This may account for the appar-

ent increased stability of **16**, as well as the more negative entropy found (−1.9 eu) for this equilibration compared with $\Delta S°$ = −0.8 eu for the equilibrium between *cis*- and *trans*-4-*tert*-butylcyclohexane carboxylic acid.[12] $\Delta H°$ for the latter process is −1.63 kcal/mol, while $\Delta H°$ for the equilibration **15** ⇌ **16** is −0.84 kcal/mol. The smaller $\Delta H°$ in this case reflects the lower activation energy required to go from equatorial to axial compared with the C-3 unsubstituted compound. Unfortunately, the nmr spectra do not permit a distinction to be made between the carboxymethylene protons in the various proposed conformations.

The equilibration of the *r*-1,*t*-3,*t*-4-dicarboxylic acid (**14**) is quite different from that of the isomeric compounds **15** and **16**. Much smaller amounts of the diaxial epimer (**20**) are formed than would be expected, the apparent $\Delta G°_{25}$ for the carboxyl being −2.9 kcal/mol (as compared with a literature value[11] of −1.1 to −1.6 kcal/mol for a carboxyl with no vicinal group). In other words, far less of the diaxial epimer is present at equilibrium than would be expected on the basis of the equilibrium constant for the C-3 unsubstituted compound. A lower $-\Delta S°_{25}$ is found for this reaction (−4.85 eu) as compared with −1.9 eu for the equilibrium **15** ⇌ **16** and −0.8 eu for the C-3 unsubstituted compound. This would suggest that the diaxial form (**20**) has more degrees of freedom than the epimer (**14**), which would be possible if **20** were to exist to some extent in the flexible form **20a**. This is likely, since the presence of two relatively large axial groups can cause the ring to equilibrate to the flexible form in order to avoid large syn-axial interactions.[16] However, **20a** would still be a much higher energy



20 **20a**

form than **14**. ΔH for the equilibrium **14** ⇌ **20** (−4.45 kcal/mol) is unusually high compared to that for the equilibrium **15** ⇌ **16** (−0.84 kcal/mol), and for the C-3 unsubstituted compound (−1.63 kcal/mol), and could be a reflection of the high energy difference between the chair and the flexible forms.

Experimental Section

4-*tert*-Butylcyclohexene-1-carboxylic Acid. 4-*tert*-Butyl-1-cyanocyclohexene (50 g) was treated with 40% sulfuric acid (500 ml) and the mixture was boiled under reflux until crystals had formed on the surface of the sulfuric acid and an oil (the nitrile) was no longer present. The mixture was cooled, diluted with water (1000 ml), and filtered. The crystalline acid (41 g, 75%) had mp 189–191° (from acetone) (lit.[17] 182–185° from acetic acid–water): ir (KBr) 3500–2500 (COOH), 1675 (C=O), 1645 cm^{-1} (C=C).

Ethyl 4-*tert*-Butylcyclohexene-1-carboxylate. 4-*tert*-Butylcyclohexene-1-carboxylic acid (70 g) was dissolved in absolute ethanol (500 ml). Sulfuric acid (30 ml) was added, and the mixture was boiled under reflux for 5 hr. The solution was cooled, diluted with water (500 ml), and extracted with ether (4 × 200 ml). The combined ether extracts were washed with 5% sodium hydroxide (3 × 200 ml) and brine (3 × 200 ml), dried ($MgSO_4$), and evaporated. The residual oil was distilled to give the ester (64 g, 70%), bp 80–82° (0.1 mm): ir (neat) 1705 (C=O), 1645 cm^{-1} (C=C); nmr (CCl_4) δ 6.85 (s, br, 1, vinyl **H**), 4.10 (q, 2, $COOCH_2CH_3$), 1.25 (t, 3, $COOCH_2CH_3$), 0.90 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.41; H, 10.54.

Addition of Diethyl Malonate to Ethyl 4-*tert*-Butylcyclohexene-1-carboxylate. Thermodynamic Control Conditions. Sodium (3.6 g, 0.156 mol) was dissolved in absolute ethanol (50 ml). Diethyl malonate (37 g, 0.23 mol, freshly distilled) and ethyl 4-*tert*-butylcyclohexene-1-carboxylate (16.4 g, 0.078 mol) were added. The solution was boiled under reflux for 24 hr. It was then cooled, acidified with glacial acetic acid, basified with 5% sodium hydroxide, and extracted with ether (3 × 100 ml). The combined ether extracts were extracted with 5% sodium hydroxide (3 × 100 ml), and brine (3 × 100 ml), dried ($MgSO_4$), and evaporated. The residual oil was fractionally distilled. The first fraction contained diethyl malonate, bp 45° (0.2 mm). The second fraction contained unreacted olefin (8 g), bp 75–85° (0.2 mm). The third fraction contained mixed malonate esters (9.5 g, 65% conversion), bp 142–155° (0.2 mm). Glc analysis (25% Apiezon on 60–100 mesh Chromosorb W, 6 ft × 3/16 in., program 210–250° at 2°/min, 60 ml/min flow rate of helium carrier gas) indicated the presence of five compounds which were subsequently shown to be three malonate adducts and two acetates (*vide infra*). The malonate adducts were present in the ratio **8:9:10** = 17:72:11, corrected for relative molar response factors, using benzanilide as internal standard. The components were separated by preparative gas chromatography using a 25% Apiezon M on 60–100 mesh Chromosorb W, 2 × 3 ft × 3/4 in. biwall column at 250° and a 300 ml/min helium carrier gas flow rate. The properties of the individual compounds are given below.

Diethyl *r*-1-*tert*-Butyl-*t*-4-carbethoxy-*c*-3-cyclohexylmalonate (9). The diequatorial ester (**9**) was obtained (3.2 g, 20%) by preparative gas chromatography as described above. It crystallized with difficulty from light petroleum (bp 30–60°), mp 30–31.5°: ir (neat) 1760, 1735 cm^{-1} (ester C=O); nmr (acetone-d_6) δ 4.15 (m, 6, $COOCH_2CH_3$), 3.70 (d, 1, J = 13 Hz, $-CH(COOEt)_2$), 3.00 (m, 1, C-3-H), 2.52 (br s, 1, C-4-H), 1.25 (m, 9, $COOCH_2CH_3$), 0.8p (s, 9, *tert*-butyl); mass spectrum (70 eV) *m/e* (rel intensity) 370 (0.3), 324 (9), 278 (9), 266 (22), 240 (18), 239 (11), 222 (12), 221 (18), 211 (30), 166 (17), 165 (28), 161 (50), 160 (100), 153 (12), 137 (23), 133 (13), 57 (18).

Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.91; H, 9.28.

***r*-1-*tert*-Butyl-*c*-3-(carboxymethyl)cyclohexane-*t*-4-carboxylic Acid (15).** The ester (**9**) (0.5 g, 1.35 mol) was hydrolyzed with boiling 3 *N* hydrochloric acid (15 ml) for 3 days. On cooling the crystals of the dicarboxylic acid (**15**) (0.19 g, 58%) were collected and recrystallized from ether–light petroleum (bp 30–60°), mp 181–182.5° (lit.[1] 181–182°); infrared spectrum identical with that of authentic material.[1]

***r*-1-*tert*-Butyl-*c*-3-(carbethoxymethyl)-*t*-4-carbethoxycyclohexane (12).** The *r*-1,*c*-3,*t*-4 acetate (**12**) (0.35 g, 1.5%) was collected by preparative gas chromatography of the thermodynamic control reaction mixture under the conditions described above, colorless liquid, bp 106–110° (0.1 mm): ir (neat) 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.06 (q, 4, J = 8 Hz, $COOCH_2CH_3$), 1.23 (t, 6, J = 8 Hz, $COOCH_2CH_3$), 0.85 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H , 10.13. Found: C, 68.20; H, 10.12.

The *r*-1,*c*-3,*t*-4 acid (**9**) (50 mg, 0.2 mmol) in absolute ethanol (3 ml) and concentrated sulfuric acid (2 drops) was boiled under reflux for 5 hr. The solution was cooled, diluted with water (3 ml), and extracted with ether (3 × 3 ml). The combined extracts were washed with 5% NaOH (2 × 3 ml) and brine (2 × 3 ml), dried ($MgSO_4$), and evaporated to give **12** (40 mg, 66%), identical with the compound obtained above.

***r*-1,*c*-3,*t*-4 Acetate (12) by Decarbethoxylation of 9.** Malonate (**9**) (0.426 g, 1.15 mmol) and 10% palladium on charcoal (0.348 g) were sealed in a tube and heated at 210° for 3 days. The contents of the tube were suspended in ether and filtered. The filtrate was evaporated to give a colorless oil (0.343 g, 92%), glc analysis (20% SE 30 on Chromosorb W, 60–100 mesh, 6 ft × 3/16 in., program 200–240°/2°/min, 60 ml/min He carrier gas) of which indicated the presence of a mixture of two acetates. The acetates were separated by column chromatography on silica gel (100 g) and eluted with light petroleum (bp 30–60°)–benzene (1:9 v/v). Fractions rich in the *r*-1,*c*-3,*t*-4 acetate were further pruified by preparative glc under the conditions described above. The *r*-1,*c*-3,*t*-4 acetate thus collected (0.155 g, 20%) had an ir spectrum and glc retention time identical with those of the *r*-1,*c*-3,*t*-4 acetate obtained above.

Diethyl *r*-1-*tert*-Butyl-*t*-4-carbethoxy-*t*-3-cyclohexylmalonate (8) was obtained in very small amounts (200 mg) from the thermodynamic control reaction mixture by preparative gas chromatography. The malonate (**8**) is a colorless liquid, bp 140–144° (0.2 mm): ir (neat) 1750, 1730 cm^{-1} (ester C=O); nmr (acetone-d_6) δ 4.15 (m, 6. $COOCH_2CH_3$), 3.65 (d, 1, J = 12 Hz, $CH(COOEt)_2$), 2.80 (m, 1, C-3-H), 2.20 (m, 1, C-4-H), 1.25 (m, 9, $COOCH_2CH_3$), 0.89 (s, 9, *tert*-butyl); mass spectrum (70 eV) *m/e* (rel intensity) 370 (19), 327 (7), 326 (34), 325 (5), 314 (4), 311 (6),

300 (4), 298 (4), 278 (9), 267 (7), 258 (6), 257 (4), 240 (8), 223 (6), 222 (6), 221 (5), 212 (6), 211 (32), 210 (42), 200 (4), 195 (7), 194 (4), 193 (5), 173 (12), 168 (6), 167 (6), 166 (11), 162 (5), 161 (52), 160 (100), 137 (13), 133 (7), 121 (7), 107 (7), 94 (9), 81 (11), 79 (11), 57 (26), 41 (17).

Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.38; H, 9.27.

***r*-1-*tert*-Butyl-*t*-3-(carboxymethyl)cyclohexane-*t*-4-carboxylic Acid (14).** **8** (0.188 g, 0.5 mmol) and 3 *N* HCl (5 ml) were boiled under reflux for 3 days. The white solid was filtered and recrystallized from ether–light petreoleum (bp 30–60°) to give the acid (34 mg, 36%), mp 193–194° (lit.[1] 190–192°); ir spectrum identical with that of authentic material.[1]

***r*-1-*tert*-Butyl-*t*-4-carbethoxy-*t*-3-(carbethoxymethyl)cyclohexane (11)** was prepared in 25% yield by the esterification of the corresponding dicarboxylic acid as described for the *r*-1,*c*-3,*t*-4 isomer. Insufficient amounts of acetate were present in the malonate reaction mixture to allow preparative glc isolation of this compound: colorless liquid, bp 88–92° (0.007 mm); ir (neat) 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.00 (q, 4, J = 8 Hz, $COOCH_2CH_3$), 1.17 (t, 6, J = 8 Hz, $COOCH_2CH_3$), 0.79 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.31; H, 10.16.

Diethyl *r*-1-*tert*-butyl-*c*-4-carbethoxy-*c*-3-cyclohexylmalonate (10) (200 mg) was obtained from the thermodynamic control reaction mixture by preparative gas chromatography as described above: mp 50.5–51.5° (from light petroleum, bp 30–60°); ir (KBr) 1730 cm^{-1} (C=O); nmr (acetone-d_6), δ 4.20 (m, 6, $COOCH_2CH_3$), 3.76 (d, 1, J = 11 Hz, $CH(COOEt)_2$), 3.05 (m, 1, C-3–H), 2.55 (m, 1, C-4–H), 1.25 (m, 9, $COOCH_3CH_3$), 0.85 (s, 9, *tert*-butyl); mass spectrum (70 eV) *m/e* (rel intensity) 326 (2), 325 (10), 324 (4), 312 (8), 280 (3), 240 (9), 223 (5), 222 (15), 221 (30), 211 (15), 210 (10), 208 (6), 207 (5), 205 (6), 195 (6), 193 (11), 161 (50), 160 (68), 155 (8), 153 (12), 149 (9), 148 (9), 139 (8), 137 (30), 135 (28), 133 (18), 121 (21), 115 (18), 93 (29), 91 (18), 87 (14), 83 (12), 81 (35), 79 (37), 69 (20), 67 (30), 57 (100).

Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.38; H, 9.27.

***r*-1-*tert*-Butyl-*c*-3-(carboxymethyl)cyclohexane-*c*-4-carboxylic Acid (16).** **10** (1.00 g, 2.7 mmol) and 3 *N* HCl (20 ml) were boiled under reflux for 3 days. The mixture was cooled and extracted with ether (2 × 30 ml). The residual solid (0.13 g, 20%) had mp 203–205° [from ether–light petroleum (bp 30–60°)] (lit.[1] 210–212°): ir (KBr) 3300–2500 (OH), 1725 cm^{-1} (C=O), identical with that of a previously obtained sample.[1] On heating with acetic anhydride for 4 hr it gave *cis*-4-*tert*-butyl-*cis*-hexahydrohomophthalic anhydride (70%): mp 104–105° (lit.[1] 113–115°); ir (KBr) 1810, 1765 cm^{-1} (cyclic anhydride C=O), identical with that of an authentic sample.[1]

***r*-1-*tert*-Butyl-*c*-4-carbethoxy-*c*-3-(carbethoxymethyl)cyclohexane (13).** The *r*-1,*c*-3,*c*-4 acetate (0.35 g, 1.5%), collected by preparative glc of the thermodynamic control reaction mixture the conditions described above, was a colorless liquid: bp 106–110° (0.1 mm); ir (neat) 1740 cm^{-1} (C=O); nmr (CCl_4) δ 4.00 (q, 4, J = 8 Hz, $COOCH_2CH_3$), 1.20 (t, 6, J = 8 Hz, $COOCH_2CH_3$), 0.85 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.01. Found: C, 68.16; H, 10.13.

It was also prepared (30% yield) by esterification of the *r*-1,*c*-3,*c*-4-dicarboxylic acid as described for the *r*-1,*c*-3,*t*-4 isomer and was identical with the cis,cis acetate obtained by preparative glc above.

***r*-1,*c*-3,*c*-4 Acetate (13) by Decarbethoxylation of 10.** This was prepared (90% yield) by decarbethoxylation of the *r*-1,*c*-3,*c*-4 malonate (**10**) as described for the *r*-1,*c*-3,*t*-4 acetate.

The Michael Addition. (a) In Toluene. Sodium (3 g, 0.13 mol) was dispersed in hot xylene, and the xylene was decanted and replaced with toluene (70 ml). Diethyl malonate (31 g, 0.19 mol) was added. When all the sodium had disappeared, the olefin (**7**) (27.3 g, 0.13 mol) was added, as was absolute ethanol (5 drops). The mixture was boiled under reflux for 48 hr, acidified with glacial acetic acid, and basified with 5% NaOH, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 100 ml), the organic extracts were combined, washed with 5% NaOH (2 × 100 ml), brine (2 × 100 ml), and then dried ($MgSO_4$). The solution was evaporated and the residual oil was fractionally distilled. The fraction bp 142–145° (0.2 mm) contained a mixture of the malonate esters (12.01 g, 25%), **8:9:10** = 1:39:60 [by glc and corrected for relative molar response factors (benzanilide, internal standard) as described above]. The mixture was partially separated into its components by preparative gas chromatography.

(b) In Ethanol under Kinetic Control Conditions. Sodium (14.2 g, 0.61 mol) was dissolved in absolute ethanol (400 ml). Diethyl malonate (149 g, 0.93 mol) and ethyl 4-*tert*-butylcyclohexene-1-carboxylate (65 g, 0.31 mol) were added and the mixture was stirred at room temperature for 4 days. Fractional distillation of the organic materials isolated gave a mixture of the isomeric malonate esters **9:10** = 33:67 [analyzed by glc and corrected for relative molar response factors (benzanilide as internal standard) as described above] (50 g, 45%), bp 140–144° (0.2 mm).

(c) In Diethyl Carbonate. Diethyl malonate (74.3 g, 0.465 mol) was added to a solution of sodium (7.53 g, 0.310 mol) in absolute ethanol (310 ml). The ethanol was distilled and replaced by diethyl carbonate (200 ml) and ethyl 4-*tert*-butylcyclohexene-1-carboxylate (32.5 g, 0.155 mol) was added. The solution was boiled under reflux for 12 hr and worked up as described above for the reaction in toluene.

Fractional distillation of the organic-soluble residue gave a mixture of malonate adducts, bp 110–124° (0.007 mm) (7.95 g, 16%), in which the ratio of **8:9:10** was 19:64:17 [analyzed by glc and corrected for relative molar response factors (benzanilide as internal standard) as previously described].

Attempted H–D Exchange in 10 at Room Temperature. The *r*-1,*c*-3,*c*-4 malonate (**10**) (0.396 g, 1.08 mmol) was dissolved in absolute ethanol (2 ml). A solution of sodium ethoxide [from sodium (0.087 g, 3.7 mmol) in absolute ethanol (4 ml)] was added. The solution was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, D_2O (2 ml) was added, and the mixture was stirred at room temperature for 10 min. The mixture was then extracted with carbon tetrachloride (3 × 5 ml), and the combined organic extracts were dried ($MgSO_4$) and concentrated. Glc analysis [20% SE 30 on Chromosorb W (60–100 mesh), 6 ft × 3/16 in., program 200–240°/2°/min; 60 ml/min He carrier gas] indicated that ethyl 4-*tert*-butylcyclohexene-1-carboxylate (**7**) was the only product formed.

H–D Exchange of the *r*-1,*t*-3,*t*-4 Malonate (8) in Ethanol at Room Temperature. **8** (40 mg, 0.11 mmol) was added to a solution of sodium (30 mg, 0.13 mmol) in ethanol (3 ml). The solution was stirred for 40 min at room temperature, the solvent was evaporated *in vacuo*, and D_2O (1 ml) was added. After 20 min the solution was extracted with carbon tetrachloride (3 × 5 ml) and the combined organic extracts were dried ($MgSO_4$) and concentrated. Glc analysis indicated the presence of one compound, whose retention time was identical with that of starting material (20 min). Its nmr spectrum was identical with that obtained from starting material except that the doublet at δ 3.65 [$CH(COOEt)_2$] was now a very broad, weak absorption: mass spectrum (70 eV) *m/e* (rel intensity) 371 (1), 370 (1), 369 (1), 355 (5), 341 (2), 327 (4), 326 (16), 325 (19), 324 (5), 298 (5), 297 (5), 283 (6), 281 (5), 279 (19), 271 (5), 270 (5), 269 (8), 268 (13), 251 (8), 241 (5), 240 (8), 227 (5), 223 (11), 222 (12), 221 (14), 211 (23), 173 (28), 162 (25), 161 (84), 160 (28), 137 (28), 81 (31), 79 (44), 57 (100).

"Equilibration" of Diethyl *r*-1-*tert*-butyl-*t*-4-carbethoxy-*c*-3-cyclohexylmalonate (9). **9** (0.25 g, 0.68 mmol) was dissolved in a solution of sodium (31 mg, 1.35 mmol) and diethyl malonate (322 mg, 2.03 mmol) in absolute ethanol (3 ml). The mixture was boiled under reflux for 19 hr. The reaction was worked up as described in the H–D exchange studies. Glc analysis indicated the presence of the three malonates **8**, **9**, and **10** in the ratio 6:78:16. The identity of the three malonates was confirmed by comparison of their infrared spectra with those of authentic materials. Similar results were obtained on "equilibration" of **10** (**8:9:10** = 7:78:15).

Equilibration of the *r*-1,*t*-3,*t*-4-Dicarboxylic Acid (14). The following general procedure was used to equlibrate the *r*-1,*t*-3,*t*-4-dicarboxylic acid (**14**). Samples of the pure acid (18–22 mg) were placed in Pyrex test tubes (10 × 75 mm). An excess of concentrated HCl (0.2 ml) was added to each sample and the tubes were sealed. The sealed tubes were heated in an oven for 16 hr. Runs were carried out at three temperatures: 178 ± 2, 198 ± 2, and 217 ± 2°. The tubes were cooled and opened, and the HCl was removed under vacuum. The contents of each tube were dissolved in absolute methanol (3 ml). Sulfuric acid (1 drop) was added, and the solution was boiled under reflux for 5 hr. It was then diluted with water (5 ml) and extracted with ether (3 × 5 ml), and the ether extracts were then dried ($MgSO_4$) and evaporated. The residual oil (10 mg) was analyzed by glc (20% SE 30 on Gas-Chrom Q, 60–100 mesh; 6 ft × 3/16 in.; program 165–210°/2°/min; 60 ml/min He carrier gas). Two peaks were observed, the smaller and first eluting being due to the *r*-1,*t*-3,*c*-4 isomer, which had a re-

tention time of 24.8 min. The second peak (retention time, 26.3 min) was due to the *r*-1,*t*-3,*t*-4-ester (11) identical with the material previously obtained[1]). No side products were formed. Esterification runs on individual acids indicated these to be essentially quantitative.

The results, which are the averages of two runs, are summarized in Table IV.

Table IV
Equilibration of the *r*-1,*t*-3,*t*-4-Dicarboxylic Acid with 12 *N* Hydrochloric Acid

T, °K	*r*-1, *t*-3, *t*-4 : *r*-1, *t*-3, *c*-4	K_{eq}
451 ± 2	92 : 8 (±1%)	11.5 ± 0.2
471 ± 2	90 : 10 (±1%)	9.0 ± 0.2
490 ± 2	88.5 : 11.5 (±1%)	7.7 ± 0.2

$\Delta H°$ and $\Delta S°$ were determined graphically using the following equations.

$$\Delta H° = \frac{-R[\ln K_2 - \ln K_1]}{(1/T_2) - (1/T_1)}$$

$$\Delta S° = \frac{RT_2 \ln K_2 - RT_1 \ln K_1}{T_2 - T_1}$$

$$\Delta H° = -4.3 \pm 0.1 \text{ kcal/mol}$$

$$\Delta S° = 4.8_5 \pm 0.02 \text{ eu}$$

$$\Delta G°_{25} = \Delta H° - T\Delta S° = -2.9 \pm 0.1 \text{ kcal/mol}$$

Equilibration of Dicarboxylic Acids 15 and 16. (a) With 5% Aqueous Sodium Hydroxide (*cf.* ref 18). Each of the pure acids (0.014–0.018 g) was placed in a Pyrex tube and treated with an excess of 5% NaOH solution (0.3 ml): the tubes were sealed and heated at 240 ± 4° for 24 hr. The solutions were acidified and evaporated to dryness, the residue was esterified with diazomethane,[1] and the esters were analyzed by glc as described above.

(b) With 12 *N* HCl. This was carried out as described above for the equilibration of **14**. The infrared spectrum of the crude reaction mixture indicated the lack of formation of any cyclic or other acid anhydride, as also did glc. The crude acids were methylated with diazomethane [as under (a) above] and analyzed.

(c) With 10% Palladium on Charcoal (*cf.* ref 19). Each of the pure acids (0.02–0.03 g) was mixed with 10% Pd–C (0.007 g) and heated in a sealed tube at 240 ± 4° for 29 hr. The products were extracted with ether (2 (2 ml) and centrifuged, and the solution was decanted (procedure repeated twice). Again no anhydride was formed. Methylation with diazomethane was followed by quantitative glc analysis.

In none of the above cases were any by-products formed nor was any evidence found that one conformer was being selectively consumed. The results are summarized in Table III.

Acknowledgment. Part of this work was supported by a grant from the Defense Research Board of Canada during the tenure (by D.L.S.) of an NRC Studentship. Another part was carried out during the tenure (by S.S.S.) of an NDEA Fellowship. We also wish to thank the Dow Chemical Co. for the gift of 4-*tert*-butylcyclohexanone.

Registry No.—**1**, 7370-14-1; **7**, 23022-33-5; **8**, 53154-24-8; **9**, 23191-42-6; **10**, 23191-41-5; **11**, 53154-25-9; **12**, 53154-26-0; **13**, 53154-27-1; **14**, 18680-01-8; **15**, 18679-93-1; **16**, 18679-94-2; 4-*tert*-butylcyclohexene-1-carboxylic acid, 31845-19-9; diethyl malonate, 105-53-3.

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The Direct Acylamination of Quinoline, Isoquinoline, Benzimidazole, Pyridazine, and Pyrimidine 1-Oxides. A Novel 1,5-Sigmatropic Shift[1]

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Received August 16, 1974

The direct acylamination of pyridine 1-oxides using an *N*-phenylbenzimidoyl chloride or the corresponding nitrilium salt has been extended to the title heteroaromatic *N*-oxides. With quinoline 1-oxide it is proposed that a novel 1,5-sigmatropic shift in the 1,2-dihydro intermediate eventually led to 3-quinolyl benzoate and to 2-anilinoquinoline. 2,6-Lutidine similarly gave 3-(2,6-dimethylpyridyl)-*N*-phenylbenzimidate. The possible mechanisms of the formation of these products are discussed.

The direct acylamination of pyridine 1-oxides using imidoyl halides or nitrilium salts has recently been reported.[2] The main by-products formed when *N*-phenylbenzimidoyl chloride was used were the corresponding 3-chloropyridine derivative and benzanilide. The present paper describes the extensions of this work to other heterocyclic systems.

Acylamination of 6-methyl- and 4,6-dimethylpyrimidine 1-oxides with *N*-phenylbenzimidoyl chloride gave low to moderate yields of the expected 2-*N*-benzoylanilino derivative together with some of the debenzoylated secondary amine (no attempt was made to optimize yields in these reactions; we believe that much higher yields of products are possible). In addition to being a synthetically useful approach to substituted 2-acylaminated pyrimidines this reaction could, in principle, be used to differentiate between isomeric unsymmetrically substituted pyrimidine 1-