from basic aluminum oxide and after solvent concentration afforded yellow needles, mp 174° dec, nmr (DMSO-d_6) δ 8.96 (d, 1, J = 11 Hz), 8.66 (m, 2), 8.2 (d, 1, J = 8 Hz), 8.01–7.47 (m, 3), 7.27 (d, 1, J = 11 Hz), each peak a doublet with J = 2 Hz. The hydrochloride was prepared by shaking a benzene solution of 60 mg (0.29 mmol) of **8** with 50 ml of aqueous 2 *N* hydrochloric acid. The acidic solution was allowed to stand overnight and yielded 42 mg (54.5%) of the salt as tiny, bright yellow needles, mp >280°. *Anal.* Calcd for $C_{13}H_{11}N_2Cl$: C, 67.68; H, 4.81; N, 12.14. Found: C, 67.20; H, 4.73; N, 11.76 (12.03).

Registry No.—**1**, 3128-77-6; **2**, 246-06-0; **3**, 950-95-8; **4**, 36146-64-2; **7**, 36118-87-3; **8**, 36118-88-4; **9**, 36118-89-5; **10**, 36118-90-8; **15**, 36146-65-3; **16** picrate, 36146-66-4; **17**, 35704-54-2; **18**, 36146-68-6; **19**, 36146-69-7; **20** HCl, 36146-70-0; **22** HCl, 36146-71-1; 1,3-dicyclohexylthiourea, 1212-29-9; 2-isocyano-2′-formamidobiphenyl, 36146-72-2; 6-oxo-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole oxime, 36146-73-3; 6-amino-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole, 36146-74-4; 8-aminocyclohept[*b*]indole, 36146-75-5; 8-aminocyclohept[*b*]indole hydrochloride, 36146-76-6.

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Stereochemistry of Nucleophilic Addition Reactions. The Addition of Thiophenol and of Hydrogen Chloride to 4-*tert*-Butyl-1-cyanocyclohexene

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The addition of thiophenoxide ion to 4-*tert*-butyl-1-cyanocyclohexene (**1**) in ethanol gives the two products **2** and **3** containing an axial thiophenoxy group. In tetrahydrofuran, **14** is also formed. The stereochemistries of the products were established by a combination of nmr spectroscopy, chemical transformations, and equilibration experiments. An explanation is proposed for the observed steric course of the addition. *r*-1-*tert*-Butyl-*t*-3-phenylsulfonyl-*c*-4-phthalimidomethylcyclohexane was found to be somewhat more stable thermodynamically than the *r*-1,*c*-3,*c*-4 isomer (**13**). The data suggest that the *r*-1,*t*-3,*c*-4 isomer exists predominantly in the twist–boat conformation (**12**). Severe repulsive gauche interactions between the $PhSO_2$ and the phthalimidomethyl group are proposed to explain the observed order of stabilities. The addition of HCl to **1** gives only *r*-1-*tert*-butyl-*t*-3-chloro-*t*-4-cyanocyclohexane in which the chlorine is axial.

The stereochemistry of the Michael and Michael-type additions to activated olefins of rigid conformation has been the object of study in our laboratories. We have already established that, under conditions of kinetic control, the diethyl malonate anion in ethanol solution adds to 4-*tert*-butyl-1-cyanocyclohexene to give the addition product with the equatorial malonate and axial cyanide group as the main isomer, with the (e)-malonate (e)-nitrile as the minor product.[1] Under conditions of thermodynamic control, the latter was the main product. No axial malonate could be detected, though small amounts of the product of "abnormal" Michael addition, ethyl *r*-1-*tert*-butyl-*t*-3-carbethoxymethyl-*c*-4-cyano-*t*-4-cyclohexanecarboxylate were isolated, resulting from the rearrangement of the initially formed axial malonate anion intermediate. In a nonprotic solvent, the main product was that of "abnormal" addition.

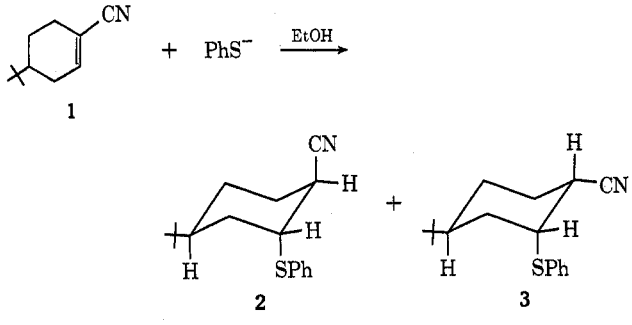
To determine whether or not the behavior of the malonate anion was representative of the mode of addition of nucleophiles in general, we embarked on a study of the addition of thiols to activated olefins chosen such that the products would have an unambiguous stereochemistry and that product mixtures could be resolved readily, the stereochemistry of the isomers established, and the isomer ratios determined quantitatively with ease. The additions of nucleophiles have been shown to be of considerable biological importance and are thought to be involved in such diverse phenomena as the carcinogenicity of α,β-unsaturated lactones,[2] carcinostatic activity of certain plant extracts,[3] stimulation of nerve endings,[4] isomerization of retinal in the visual process,[5] the action of oral contraceptives,[6] and the bacteriostatic activity of naphthoquinones.[7] It is obvious that a knowledge of the steric course of such additions could lead to the design of molecules which could better approach and fit into the active site of the biologically important molecules.

The addition of *p*-toluenethiol to 1-*p*-tolylsulphonylcyclohexene under mildly basic conditions gave mainly the thermodynamically less stable cis isomer, namely *cis*-2-*p*-tolylmercapto-1-*p*-tolylsulfonylcyclohexane.[8] Since chair–chair interconversion can occur in the final products, however, nothing can really be said definitely about the preferred mode of approach of the thiolate anion in this system under conditions of kinetic control. In contrast to the above reaction, addition of *p*-toluenethiolate to 1-*p*-tolylsulfonylcyclopentene gave the trans product, which was explained on the basis of steric interaction between the arylsulfonyl group and the arylmercapto group in the cyclopentyl intermediate anion.[9]

When thiophenoxide ion was added to 4-*tert*-butyl-1-cyanocyclohexene (**1**) in ethanol two products were formed which were resolved by gas chromatography

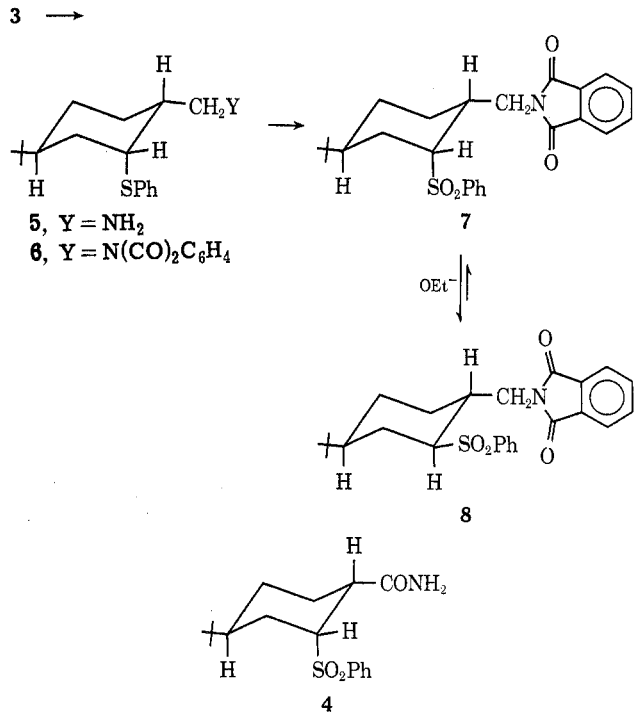
(1) R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).
(2) J. B. Jones and J. M. Young, *Can. J. Chem.*, **46**, 1859 (1968); J. B. Jones and J. N. Baker, *ibid.*, **48**, 1574 (1970).
(3) S. M. Kupchan, *Trans. N. Y. Acad. Sci.*, **32**, 85 (1970); S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. J. Giacobbe, *Science*, **168**, 876 (1970); S. M. Kupchan, C. W. Siegal, M. J. Natz, J. A. Saenz Renaud, R. C. Haltiwanger, and R. F. Bryan, *J. Amer. Chem. Soc.*, **92**, 4476 (1970).
(4) R. F. Silver, K. A. Kerr, P. D. Frandsel, S. J. Kelly, and H. L. Holmes, *Can. J. Chem.*, **45**, 1001 (1967).
(5) F. M. Menger and J. H. Smith, *J. Amer. Chem. Soc.*, **91**, 4211 (1968).
(6) E. V. Jensen, quoted in *Chem. Eng. News*, **45**, 44 (March 27, 1967).
(7) R. F. Silver and H. L. Holmes, *Can. J. Chem.*, **46**, 1859 (1968).
(8) W. E. Truce and A. J. Levy, *J. Amer. Chem. Soc.*, **83**, 4641 (1961).
(9) W. E. Truce and A. J. Levy, *J. Org. Chem.*, **28**, 679 (1963).

and shown to be *r*-1-*tert*-butyl-*t*-3-thiophenoxy-*c*-4-cyanocyclohexane (**2**) and *r*-1-*tert*-butyl-*t*-3-thiophenoxy-*t*-4-cyanocyclohexane (**3**), the products of axial addition of thiophenol to the olefin. The ratio of **2**:**3** varied with time and could be conveniently followed by glc. Under conditions of kinetic control (boiling ethanol, 16 hr) the ratio of **2**:**3** was 1:52, but as the reaction time increased this ratio gradually changed until after 70 hr (thermodynamic control conditions, equilibration) it dropped to 1:1.97. Further heating did not lead to any change in the **2**:**3** ratio. This corresponds to $\Delta G^0_{78} = -0.47$ kcal/mol for the CN group, which agrees quite well with the reported value of −0.25 kcal/mol (at 66°).[10] Clearly, the two products formed are epimeric about the $-HC_4CN$ group, with **2** presumably having the axial nitrile group.



The conformations of **2** and **3** followed readily from their nmr spectra. In the spectrum of **2** the C_3 (>CH-SPh) proton appeared as a narrow unresolved multiplet at δ 3.70, while the C_4 H also gave rise to an unresolved multiplet at 2.79, indicating the axial configuration of the substituents at C_3 and C_4 in this molecule. In **3**, on the other hand, while the C_3 H is still equatorial (doublet at δ 3.59, J_{ae} = 3 Hz), the C_4 H is axial and gives rise to a doublet of triplets at higher field [δ 2.72 (J_{aa} = 12, J_{ae} = 3 Hz)] than the corresponding equatorial proton. Consequently, the thiophenoxy group is axial in both **2** and **3**, and the nitrile group is equatorial in **3**, confirming the equilibration result.

The axial configuration of the thiophenoxy group in **3** was also established by chemical means. An attempt to oxidize **3** to the corresponding cyano sulfone with 30% hydrogen peroxide in acetic acid gave, instead, the amide sulfone (**4**), which was resistant to acid hydrolysis with 6 *N* HCl. The nitrile group in **3** was reduced with lithium aluminum hydride to the primary amine (**5**) (nonepimerizable with base) which was protected as its phthalimide (**6**), and the sulfide oxidized to the sulfone (**7**). As expected from the fact that $\Delta G^0 = -2.6$ kcal/mol for $PhSO_2-$,[10] when **7** was heated with sodium ethoxide in ethanol it was converted in over 90% yield to the diequatorial conformer **8** (some cleavage of the phthalimido group occurred under these conditions but the phthalimidomethyl group was regenerated by heating the crude reaction mixture with phthalimide). The nmr spectra of **5**, **6**, and **7** (see below) confirmed that the transformations **3** → **7** had occurred with no inversions of configuration, so that the thiophenoxy group must have been axial in **3** (and hence in **4** as well since **3** and **4** are only epimeric about C_4). While **7** and **8** had almost identical ir spectra, their nmr spectra supported their epimeric nature about C_3, for **7** exhibited a narrow band at δ 3.37 due to the C_3 H, while the corresponding absorption in **8** was much broader (but still unresolved) and appeared at higher field, 3.08.

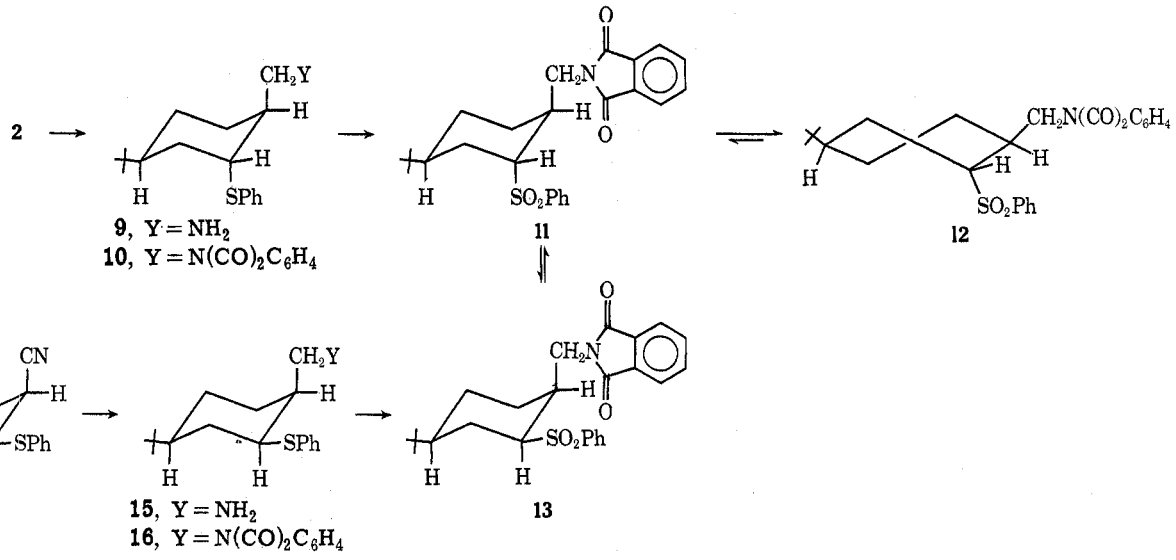


The same sequence of reactions was carried out with isomer **2** to yield the sulfone phthalimide presumed to have conformation **11**. This, however, could not be equilibrated to **13** under the conditions used for the epimerization of **7** (nor did the C_3 proton undergo H–D exchange with EtOD and EtO^-) and much more vigorous conditions were required, *e.g.*, sodio ethylene glycolate in ethylene glycol at 130°, to effect this equilibration. The epimer ratio at equilibrium was thus found to be 60:40 **11**:**13**; *i.e.*, the "axial" phenylsulfonyl configuration was preferred over the equatorial one! The nmr spectra of **9** and **10** (see below) confirmed that no inversion of configuration had taken place up to that point and, in view of the equilibration results, the possibility was considered that epimerization could have occurred in the oxidation step **10** → **11**.[11]

This could be readily discounted when it was found that, when the addition of thiophenoxide ion to **1** was carried out in boiling tetrahydrofuran, a third isomer was isolated whose nmr confirmed it to be the product of equatorial addition of PhS^-, followed by equatorial protonation to give *r*-1-*tert*-butyl-*c*-3-thiophenoxy-*c*-4-cyanocyclohexane (**14**). Thus the C_3 H appeared as a doublet of triplets at δ 2.95 (J_{aa} = 15, J_{ae} = 4 Hz) (axial proton), 0.7 ppm upfield from the C_3 H absorption in **2** and **3**, and the C_4 H was a narrow unresolved multiplet at 2.76 (equatorial proton). The ratio of **2**:**3**:**14** formed in this reaction was 31:62:7 (85% overall yield). When the addition was carried out in boiling dimethylformamide solution, the ratio of **2**:**3**:**14** was 29:27:44 (69% overall yield), the higher reaction temperature apparently favoring the formation of more of the thermodynamically more stable isomer (ΔG^0_{25}

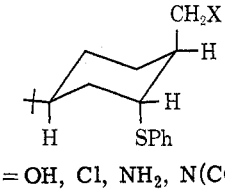
(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 436.

(11) J. A. Claisse, D. I. Davies, and C. K. Alden, *J. Chem. Soc. C*, 1498 (1966).

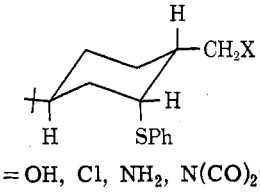


for PhS is −0.8 kcal/mol[10]), since the Michael-type addition is readily reversible (treatment of either **2** or **3** with OEt^- in EtOH causes appreciable reversal to **1** and thiophenol; if thiophenol was added to suppress the reversal then **2** and **3** could be equilibrated with base). **14** could be reduced to the primary amine **15** which was then protected as **16** and oxidized to give **13** so that all four possible sulfone phthalimides were now available. Equilibration of **13** with $NaOCH_2CH_2OH$ in ethylene glycol at 130° gave the same equilibrium mixture of **11** and **13** as was obtained above from **11**, *i.e.*, with the "axial" isomer predominating.

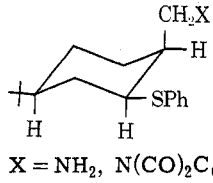
The nmr spectra of the intermediates in these transformations were quite instructive. Thus, the equatorial C_3 H protons in **5**, **6**, **9**, and **10** all appeared as narrow unresolved singlets at δ 3.38–3.70, while the axial C_3 H proton in **15** gave a broad triplet (J_{aa} = 14, J_{ae} = 4 Hz) at 3.18. From this and other[12] work a number of compounds of the general type **17**, **18**, and **19** have become available. It was observed that, in



17, X = OH, Cl, NH_2, $N(CO)_2C_6H_4$



18, X = OH, Cl, NH_2, $N(CO)_2C_6H_4$



19, X = NH_2, $N(CO)_2C_6H_4$

18 and **19**, the exocyclic methylene protons appear as the AB multiplet (eight lines) (J_{AB} = ±13.5–14.0 Hz) of an ABX system, owing to the anisotropic effect[13] of the vicinal thiophenoxy group on this methylene group which must not be able to undergo completely free rotation. On the other hand, the exocyclic methylene in compounds **17** exhibited a doublet (A_2X), the thiophenoxy group being too far from the methylene group to influence it (thereby also confirming the proposed stereochemistries). A first-order analysis of the ABX three spin system in **18** [X = $N(CO)_2C_6H_4$] (J_{AB} = 14 Hz) in $CDCl_3$ yielded the following values: J_{AX} = 10.5 Hz, J_{BX} = 4.5 Hz, and $\nu_A - \nu_B$ = 0.21 ppm. The coupling constants and chemical shifts were only slightly affected by the use of a higher dielectric constant solvent, *i.e.*, nitrobenzene: J_{AX} = 9.38 Hz, J_{BX} = 3.62 Hz, and $\nu_A - \nu_B$ = 0.22 ppm.

On the basis of these observations one could predict that, should they maintain their chair conformations, the exocyclic methylene group in sulfone phthalimides **7**, **8**, and **13** should give rise to *ABX* (*AMX*) multiplets while that in **11** should approximate an A_2X system. In actual practice, sulfone phthalimides **7**, **11**, and **13** exhibited *ABX* octets while **8** gave rise to an *AMX* pattern of lines. The fact that **11** does not give rise to the expected A_2X system suggested that the molecule might not exist in the chair form but in a twist-boat form, as does also the observation that it is thermodynamically somewhat more stable than **13**. Table I summarizes the nmr parameters for the four sulfone phthalimides.

To account for the fact that **7** is epimerized to **8** almost quantitatively under relatively mild conditions while **11** requires much more vigorous conditions to equilibrate to **13**, and also to explain the fact that **11** is somewhat thermodynamically more stable than **13**, we propose (i) that **11** actually prefers to exist in a twist-boat conformation and (ii) that there are severe repulsive gauche or torsional interactions between the bulky $PhSO_2$ and phthalimidomethyl groups in **7**, **8**, and **13**. The latter would be the same for all three if they existed in classical chair forms. This is unlikely to be the case since the *tert*-butyl-cyclohexane ring is appreciably flattened.[14] The influence of such gauche interactions

(12) R. A. Abramovitch and S. S. Singer, unpublished results.

(13) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution N.M.R. Spectroscopy," Vol. 2, Pergamon Press, Oxford, 1966, p 817.

(14) R. A. Wohl, *Chimia*, **18**, 219 (1964); F. Shah-Malak and J. H. P. Utley, *Chem. Commun.*, 69 (1967).

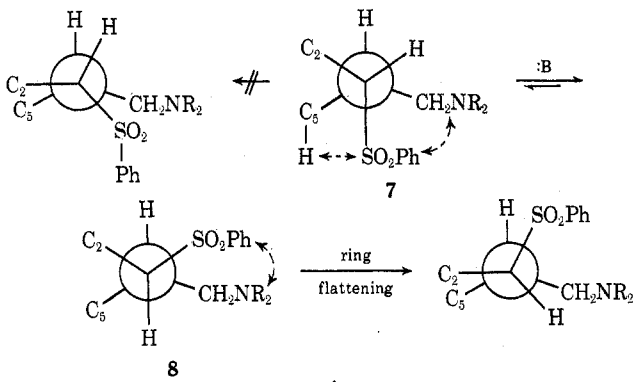
TABLE I

NMR PARAMETERS FOR C_3 H AND EXOCYCLIC METHYLENE GROUP IN SULFONE PHTHALIMIDES 7, 8, 11, AND 13 IN $CDCl_3$

Compd	δ (J in Hz) C_3 H	δ (J in Hz) $-CH_2X$	First-order analysis of $-CH_2X$, J in Hz, ν − ν in ppm
7	3.67 (e)	3.83, 4.67 (J_{AB} = 13.5)	J_{AX} = 9.46, J_{BX} = 2.04, $\nu_A - \nu_B$ = 0.32
8	3.03 (a)	3.83, 4.78 (J_{AM} = 13.5)	J_{AX} = 4.5, J_{MX} = 10.5, $\nu_A - \nu_M$ = 0.94 (J_{AX} = 3.5, J = 10.5, $\nu_A - \nu_M$ = 1.04)[a]
11	2.78 (br d, J = 6)	3.50 (J_{AB} = 14)	J_{AX} = 9.61, J_{BX} = 4.38, $\nu_A - \nu_B$ = 0.25
13	3.12 (a) (d of t, J_{aa} = 14, J_{ae} = 5)	4.20	Not analyzed

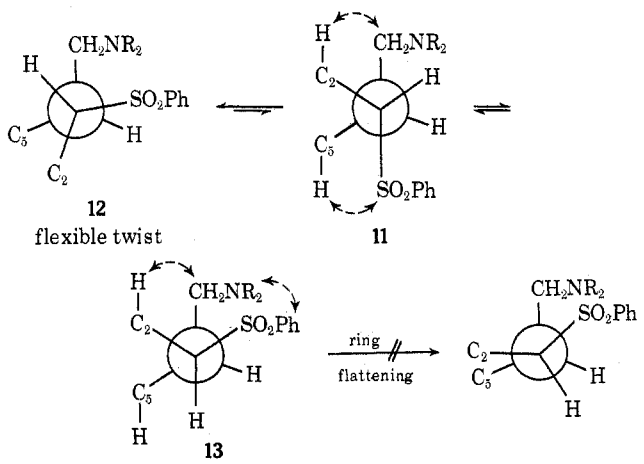
[a] In nitrobenzene solution.

may be seen from a consideration of Newman projections of the conformations about the C_3–C_4 bond. Though it is appreciated that ring flattening of cyclohexanes involves an opening of the internal ring angles resulting in "pinching" of the external angles, it is felt that Newman projections can, with this understanding, lead to a clearer—though approximate—picture of the interactions involved. Ring flattening causes the C_3 and C_4 substituents to move closer together in **7**, but further apart in **8**. This, combined with the syn-axial



R_2 = phthaloyl

interactions of $PhSO_2$ in **7**, explains the almost quantitative epimerization **7** → **8**. With the *r*-1,*c*-3,*c*-4 sulfone phthalimide **13** ring flattening would again in-

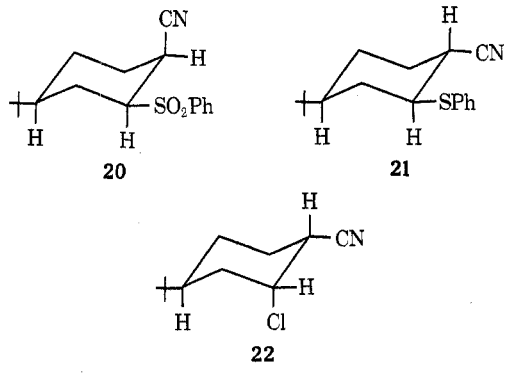


crease the important axial–equatorial torsional interaction between the phenylsulfonyl and phthalimidomethyl groups so that flattening would be hindered. While no such large gauche interaction between these groups can be present in **11** in the chair form, the syn-axial interactions must be large and a minimum value of 4.4 kcal/mol is estimated for the combined syn-axial interactions of the $PhSO_2$ and phthalimidomethyl groups. This should lead to the *r*-1,*t*-3,*c*-4 isomer existing predominantly in the twist-boat conformation (**12**), in which the three bulky groups would be pseudoequatorial, thus relieving the strain due to the diaxial functions in **11**.[15] One sufficiently large axial group, as that in *c*-4-*tert*-butyl-1-phthalimidocyclohexane, is sufficient to cause the molecule to exist largely in the twist conformation.[16] The flexibility of **12** would permit the $PhSO_2$ and $CH_2N(CO)_2C_6H_4$ groups to move apart further than they would be in **13**, so that, if the postulated gauche interaction is sufficiently large, **12** would be thermodynamically more stable than **13**, as is observed. Other examples of the reversal of a group's usual preferred configuration due to vicinal interactions with another function are known.[17] While a flattened distorted chair form of **11** might also explain some of the observations, it appears to us to be more strained than **12**, as well as not being able to account for the observed order of thermodynamic stabilities.

Support for the twist conformation comes from the nmr spectrum of the *r*-1,*t*-3,*c*-4 isomer. This conformation, but not the chair, would account readily for the fact that the exocyclic methylene group gives rise to an *ABX* spectrum rather than an A_2X one. Also the C_3 methine proton appears as a broad doublet (J = 6 Hz), which coupling constant is about twice that expected for an e,e coupling[18,19] but is reasonable for the coupling expected in a twist conformation such as **12**,[16,20,21] though no data are available at this time which would permit an evaluation of the influence of the electronegativity of the $PhSO_2$ group on the vicinal coupling constants to be made.

As mentioned above, selective oxidation of **3** to the corresponding cyano sulfone could not be achieved with hydrogen peroxide, the oxidation going all the way to the amide sulfone **4**. Oxidation to the desired sulfone nitrile could be effected with potassium permanganate. On the other hand, the *r*-1,*c*-3,*c*-4 nitrile sulfide (**14**) could be readily converted to the expected nitrile sulfone (**20**) with peracetic acid, but, unlike **2** and **3**, could not be epimerized with base to give the diequatorial isomer **21**.

(15) D. L. Robinson and D. W. Theobald, *Quart. Rev. Chem. Soc.*, **21**, 314 (1967).
(16) H. Booth and G. C. Gidley, *Tetrahedron Lett.*, 1449 (1964).
(17) D. J. Pasto and D. R. Rao, *J. Amer. Chem. Soc.*, **92**, 5151 (1970).
(18) Reference 10, p 152.
(19) E. L. Eliel, personal communication.
(20) E. Garbisch and D. Patterson, *J. Amer. Chem. Soc.*, **85**, 3228 (1963).
(21) E. L. Eliel, *Accounts Chem. Res.*, **3**, 1 (1970).



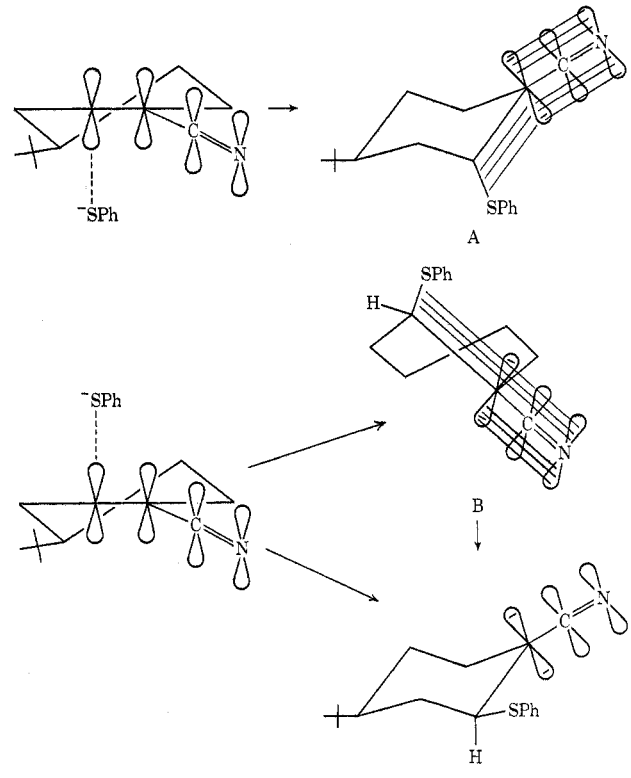
The addition of hydrogen chloride to **1** was also studied. Only one adduct was obtained, namely, *r*-1-*tert*-butyl-*t*-3-chloro-*t*-4-cyanocyclohexane (**22**), whose conformation was assigned on the basis of its nmr spectrum. The C_3 H proton appeared as a narrow unresolved band at δ 4.60 (equatorial proton, CR_2HCl), while the C_4 H gave rise to a doublet of triplets (axial proton, CR_2HCN) at 2.85 (J_{aa} = 7.5, J_{ae} = 2.5 Hz). This result is also in accord with the report[22] that the addition of HCl or DCl to 1-acetylcyclohexene gives the product of trans-diaxial addition only. The attempted addition of 48% HBr to **1** only led to the formation of 4-*tert*-butylcyclohexene-1-carboxamide.

The displacement of bromide by thiophenoxide ion from *cis*-4-*tert*-butyl-1-bromocyclohexane was shown to be an SN2 process, leading to a 1:1 mixture of *t*-4-*tert*-butyl-1-thiophenoxycyclohexane and 4-*tert*-butyl-1-cyclohexene.[23] When **22** was treated with thiophenoxide ion in a variety of solvents no direct displacement of the chlorine could be observed; instead elimination of the elements of hydrogen chloride occurred to give **1**. This is not unexpected in view of the fact that base-catalyzed trans-diaxial elimination of HCl from **22** should be a very facile process. In tetrahydrofuran solution, β elimination was followed by addition of thiophenol to the olefin to give a mixture of **2**, **3**, and **14**, as described earlier.

The present results show that, contrary to the behavior of the malonate anion which adds to **1** equatorially under conditions of kinetic control, both thiophenoxide and chloride ions prefer to add axially. 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 other factors obtaining in such additions would assume control of the guidance mechanism. In particular, axial approach to the nucleophile leads to almost continuous overlap between the developing σ bond and the conjugated system in the formation of the transition state A. For similar overlap to occur in the transition state B leading to equatorial addition the molecule would have to assume a boat-like conformation, so that this is avoided under conditions of kinetic control unless the 1,3-diaxial repulsions are large. Under conditions of thermodynamic control, some equatorial thiophenoxy adduct is formed.

(22) G. Armstrong, J. A. Blair, and J. Homer, *Chem. Commun.*, 103 (1968).

(23) E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.*, **81**, 1949 (1959).



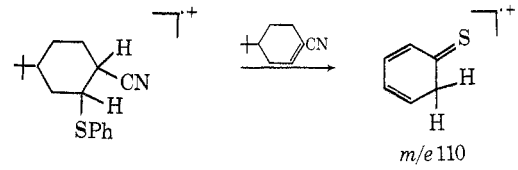
Mass Spectra of Isomeric *tert*-Butyl-4-cyano-3-thiophenoxycyclohexanes.—The three isomers, **2**, **3**, and **14**, gave similar fragmentation patterns (Table II). They all exhibited a parent ion at *m/e* 273, but

TABLE II

MASS SPECTRAL DATA FOR *r*-1-*tert*-BUTYL-4-CYANO-3-THIOPHENOXYCLOHEXANES AT 70 eV

	Relative intensity		
m/e	**2**	**3**	**14**
274	4	2.5	10
273	17	9	44
217	2	2	7
216	8	6	29
164	2.5	2	11
148	4.5	3	6.5
121	6.5	4.5	10
111	9	9	9
110	100	100	100
109	9	9	15
108	11	7	26
107	4.5		
106	4		
57	63	50	75

it is noteworthy that **14**, which cannot undergo axial elimination of PhS· gives a much more intense M^+ peak than do the other two. Other peaks are also more intense for **14**. Loss of *tert*-butyl occurs in all cases to give the *m/e* 216 ion and *tert*-Bu^+ at *m/e* 57. Loss of PhS· occurs to a small extent leading to *m/e* 164, but the major fragmentation pathway involves the formation of the olefin and what is probably the charged thiophenol tautomer (*m/e* 110) as the base



m/e 110

peak. This type of fragmentation has been found to occur in various alkylaryl thio ethers, *e.g.*, thioanisole.[24]

Experimental Section

Lithium thiophenolate was prepared by dissolving thiophenol (28 g, 0.27 mol) in toluene (25 ml), adding small pieces of lithium ribbon (1.7 g, 9.24 g-atoms) and boiling the mixture under reflux. It was then filtered; the solid was passed through a 35 mesh sieve to remove unreacted lithium and used without further purification.

Addition of Thiophenol to 4-*tert*-Butyl-1-cyanocyclohexene. A. In Ethanol.—Thiophenol (4.4 g, 0.04 mol) was added to a solution of sodium (0.07 g, 0.0033 g-atom) in anhydrous ethanol (50 ml) under nitrogen. To this solution was added 4-*tert*-butyl-1-cyanocyclohexene[1] (5 g, 0.032 mol) and the solution was boiled under reflux for 48 hr. At various intervals of time, aliquots were analyzed by glc using a 3 ft × 0.25 in 15% asphalt on Chromosorb W column and the ratio of **3**:**2** was determined: 16 hr, 52.5; 26 hr, 14.7; 48 hr, 11.0; 70 hr, 1.97; 90 hr, 1.97. The best yields (70–80%) of adducts were obtained after 48 hr. The solvent was evaporated, the mixture dissolved in chloroform and washed with 5% aqueous NaOH, and the solvent dried ($MgSO_4$) and evaporated. The residue was distilled at 170–180°(0.5 mm), and the distillate solidified partially on cooling. Crystallization from pentane gave ***r*-1-*tert*-butyl-*t*-4-cyano-*t*-3-thiophenoxycyclohexane (3)**: mp 53.5–54°; ir (KBr) 3060, 3040, 2950, 2900, 2850, 2210 cm^{-1} (C≡N); *m/e* 273 (9) (M^+).

Anal. Calcd for $C_{17}H_{23}NS$: C, 74.67; H, 8.48. Found: C, 74.31; H, 8.18.

The residue from the recrystallization was subjected to preparative glc on a 5 ft × 0.25 in 20% Apiezon M on Chromosorb P column to give **2** as an oil which was purified by molecular distillation. This gave pure ***r*-1-*tert*-butyl-*c*-4-cyano-*t*-3-thiophenoxycyclohexane (2)**: bp 125–130° (0.05 mm); ir (film) 3060, 2960, 2870, 2240 cm^{-1}; *m/e* 273 (17) (M^+).

Anal. Calcd for $C_{17}H_{23}NS$: C, 74.67; H, 8.48. Found: C, 74.45; H, 8.60.

B. In Tetrahydrofuran.—4-*tert*-Butyl-1-cyanocyclohexene (1.1 g, 6.8 mmol), lithium thiophenolate (0.72 g, 6 mmol), and thiophenol (1 g, 9 mmol) were dissolved in dry tetrahydrofuran (10 ml), and the solution was boiled under reflux for 4 hr. It was then poured into water (10 ml); the aqueous layer was extracted with ether (3 × 20 ml) and combined with the organic layer. This was washed with 5% aqueous NaOH (3 × 20 ml) and brine (3 × 20 ml), dried ($MgSO_4$), and evaporated to give a yellow oil (1.60 g), glc analysis of which (20% SE-30 on Chromosorb W, 60–100 mesh; 6 ft × $^3/_{16}$ in.; 245°; 60 ml/min He carrier gas) indicated the presence of **2**, **3**, and **14** in the ratio of 31:62:7 and a small amount of starting olefin.

The oil was chromatographed on silica gel (100 g) and eluted with petroleum ether (bp 30–60°)–benzene (1:1 v/v). Isomer **2**, bp 125–130°(0.05 mm), was eluted first, followed by ***r*-1-*tert*-butyl-*c*-4-cyano-*c*-3-thiophenoxycyclohexane**: mp 93–94.5° (petroleum ether); ir (KBr) 3050, 3030, 2925, 2850, 2200 cm^{-1}; *m/e* 273 (39) (M^+).

Anal. Calcd for $C_{17}H_{23}NS$: C, 74.67; H, 8.48. Found: C, 74.60; H, 8.59.

Further elution with the same solvent gave **3**, mp 53.5–54°.

C. In Dimethylformamide.—4-*tert*-Butyl-1-cyanocyclohexane (16.3 g, 0.1 mol), lithium thiophenolate (11.7 g, 0.1 mol), and thiophenol (33 ml, 0.3 mol) in dimethylformamide (150 ml) were boiled under reflux for 3.5 hr and worked up as described for the tetrahydrofuran reaction. Glc analysis showed the ratio of **2**:**3**:**14** to be 29:27:44. The products (18.7 g, 69%) were resolved preparatively by column chromatography on silica gel as above.

***r*-1-*tert*-Butyl-*t*-3-phenylsulfonyl-*t*-4-carboxamide (4)**.—To a solution of **3** (4 g) in glacial acetic acid (25 ml) was added 30% hydrogen peroxide (5.5 ml) followed by a few drops of concentrated H_2SO_4. The reaction mixture heated up considerably and was cooled in water. After being kept at room temperature for 0.5 hr the solution deposited crystals which were filtered, washed with water and recrystallized from methanol to give the **carboxamide** (4.2 g): mp 173–175°; ir (KBr) 3540, 3400, 3175 (NH_2), 1685 (CO), 1360, 1130 cm^{-1} (SO_2).

Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.21; H, 7.80; N, 4.34. Found: C, 63.48; H, 7.60; N, 4.31.

***r*-1-*tert*-Butyl-*t*-4-cyano-*t*-3-phenylsulfonylcyclohexane.**—A solution of potassium permanganate (2.85 g) in water (50 ml) was slowly added with stirring to the thiophenoxy nitrile **3** (1.29 g) in glacial acetic acid (8 ml). The solution was stirred for 45 min and then treated with a saturated aqueous sodium bisulfite solution until the color was discharged. The solid was filtered and dissolved in benzene (100 ml); the benzene solution was washed with water and then brine and dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the residue from petroleum ether (bp 60–80°)–benzene gave the **nitrile sulfone** (1.0 g, 70%): mp 145.5–147.5°; ir (KBr) 2250 (C≡N), 1290, 1135 cm^{-1} (SO_2).

Anal. Calcd for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59. Found: C, 66.83; H, 7.84.

***r*-1-*tert*-Butyl-*t*-4-phthalimidomethyl-*t*-3-thiophenoxycyclohexane (6)**.—**3** (4.37 g, 15.9 mmol) was added to a suspension of lithium aluminum hydride (1.15 g, 32.6 mol) in ether (50 ml) and the mixture heated under reflux for 13 hr. It was then cooled and decomposed with water and then filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated to dryness, and the residue, dissolved in benzene (50 ml), was treated with phthalic anhydride (2.47 g, 16.9 mmol) and triethylamine (0.5 ml) and boiled under reflux for 24 hr using a Dean-Stark water separator. The mixture was then washed with brine (20 ml), dried ($MgSO_4$), and evaporated, and the product recrystallized from alcohol to give the **phthalimide 6** (4.8 g, 74%): mp 145–146°; ir (KBr) 1765, 1705 cm^{-1}.

Anal. Calcd for $C_{25}H_{29}NO_2S$: C, 73.67; H, 7.17; N, 3.43. Found: C, 73.72; H, 7.14; N, 3.77.

***r*-1-*tert*-Butyl-*t*-4-aminomethyl-*t*-3-thiophenoxycyclohexane (5)**.—A mixture of the above phthalimide (4.02 g) and hydrazine hydrate (2.1 ml) in ethanol (100 ml) was boiled under reflux for 6 hr. The ethanol was distilled off and benzene added simultaneously. 1,4-Phthalazdione was filtered; the filtrate was washed with water (60 ml) and brine (30 ml), dried ($MgSO_4$), and evaporated. The residue was distilled under vacuum to give the **amine** (2.96 g, 86%), bp 131–133° (0.02 mm).

Anal. Calcd for $C_{17}H_{27}NS$: C, 73.60; H, 9.81. Found: C, 73.81; H, 9.64.

***r*-1-*tert*-Butyl-*t*-3-phenylsulfonyl-*t*-4-phthalimidomethylcyclohexane (7)**.—A mixture of **5** (4.99 g), 30% aqueous hydrogen peroxide (10 ml), concentrated H_2SO_4 (0.1 ml), and glacial acetic acid (40 ml) was stirred at room temperature for 6 hr. The solid which separated was filtered, washed with water (40 ml), and recrystallized from ethanol to give **sulfone phthalimide 7** (5.03 g, 98%): mp 193–194°; ir (KBr) 1285, 1130 cm^{-1} (SO_2).

Anal. Calcd for $C_{25}H_{29}NO_4S$: C, 68.31; H, 6.65; N, 3.18. Found: C, 68.27; H, 6.42; H, 3.25.

***r*-1-*tert*-Butyl-*t*-4-aminomethyl-*t*-3-phenylsulfonylcyclohexane.**—The above sulfone phthalimide (5.42 g) and hydrazine hydrate (5 ml) were boiled under reflux in ethanol (100 ml) for 15 hr. The ethanol was evaporated, the residue extracted with hot benzene (100 ml) and the benzene solution washed successively with water (3 × 30 ml) and brine (30 ml) and dried ($MgSO_4$). Removal of the solvent and recrystallization of the residue from cyclohexane afforded the amine (3 g, 78%): mp 115.5–117°; ir (KBr) 3380, 1290, 1125 cm^{-1}.

Anal. Calcd for $C_{17}H_{27}NO_4S$: C, 65.92; H, 8.79. Found: C, 65.94; H, 8.90.

***r*-1-*tert*-Butyl-*c*-4-phthalimidomethyl-*t*-3-thiophenoxycyclohexane (10)**.—A solution of lithium aluminum hydride (0.285 g) in dry ether (3 ml) was added dropwise under N_2 to *r*-1-*tert*-butyl-*c*-4-cyano-*t*-3-thiophenoxycyclohexane (**2**) (0.50 g) in dry ether (5 ml). The mixture was stirred and boiled under reflux for 15 hr, the excess hydride decomposed with ethanol, the mixture filtered through Celite and the filter cake washed with benzene (4 × 20 ml). The combined filtrates were dried ($MgSO_4$) and evaporated to give the amine as an oil (0.424 g): ir (KBr) 3350, 3280 (NH_2), 3065, 3055 (Ar H), 2960, 2860 cm^{-1}; nmr (CCl_4) δ 7.20 (m, 5 H, Ar H), 3.68 (br s, 1 H, C_3 H), 2.68 (br d, 2 H, CH_2NH_2), 0.90 (s, 9 H, *tert*-butyl). The pure **amine** had bp 155° (0.2 mm).

Anal. Calcd for $C_{17}H_{27}NS$: C, 73.60; H, 9.81. Found: C, 73.42; H, 9.71.

The crude amine (0.424 g) was dissolved in benzene (35 ml), and phthalic anhydride (0.42 g) and triethylamine (1 ml) were added. The mixture was boiled under reflux for 15 hr using a

(24) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 288.

Dean-Stark water separator. It was then washed with 1 *N* HCl (3 × 20 ml) and brine (3 × 20 ml), dried ($MgSO_4$), and evaporated. The residue was recrystallized from aqueous ethanol to give the **phthalimide** (0.205 g, 33%): mp 91.5–93.5°; ir (KBr) 1770, 1702 cm^{-1}; nmr (CCl_4) δ 7.80, 7.10 (m, 9 H, Ar H), 3.68 (br d, 2 H, CH_2NR_2), 3.38 (br s, 1 H, C_3 H), 0.90 (s, 9 H, *tert*-butyl); *m/e* 407 (9) (M^+).

Anal. Calcd for $C_{25}H_{29}NO_2S$: C, 73.67; H, 7.17. Found: C, 73.14; H, 7.06.

***r*-1-*tert*-Butyl-*t*-3-phenylsulfonyl-*c*-4-phthalimidomethylcyclohexane** (11).—The *r*-1,*t*-3,*c*-4-thiophenoxyphthalimide (1.05 g) in glacial acetic acid (25 ml) was oxidized at room temperature for 6 hr with 30% hydrogen peroxide (1.5 ml) and concentrated H_2SO_4 (2 drops). The product was recrystallized from aqueous ethanol to give the **sulfone** (0.97 g, 60%): mp 162.5–163.5°; ir (KBr) 1770, 1705 (C=O), 1300, 1140 cm^{-1} (SO_2).

Anal. Calcd for $C_{25}H_{29}NO_4S$: C, 68.31; H, 6.65. Found: C, 67.97; H, 6.41.

***r*-1-*tert*-Butyl-*c*-4-phthalimidomethyl-*c*-3-thiophenoxycyclohexane** (16).—*r*-*tert*-Butyl-*c*-4-cyano-*c*-3-thiophenoxycyclohexane (**14**, 1.38 g) was reduced with $LiAlH_4$ in the same manner as was **2** to give the amine **15** (1.29 g, 92%): ir (film) 3350, 3280 cm^{-1} (NH_2); nmr (CCl_4) δ 7.20 (m, 5 H, Ar H), 3.20 (m, 4 H, CH_2NH_2, 2 H exchangeable with D_2O), 2.60 (t, J_{aa} = 11 Hz, 1 H, C_3 H), 0.96 (s, 9 H, *tert*-butyl).

The crude amine (0.82 g) was treated with phthalic anhydride as before to give the **phthalimide** (0.883 g, 74%): mp 111–112° (aqueous EtOH); ir (KBr) 1770, 1710 cm^{-1}.

Anal. Calcd for $C_{25}H_{29}NO_2S$: C, 73.67; H, 7.17. Found: C, 73.84; H, 7.29.

***r*-1-*tert*-Butyl-*c*-3-phenylsulfonyl-*c*-4-phthalimidomethylcyclohexane** (13).—Phthalimide **16** (1.3 g) was oxidized as usual with hydrogen peroxide to give the **sulfone** (1.04 g, 73%): mp 204.5–205°; ir (KBr) 1770, 1710 (C=O), 1305, 1145 cm^{-1} (SO_2).

Anal. Calcd for $C_{25}H_{29}NO_4S$: C, 68.51; H, 6.65. Found: C, 68.50; H, 6.75.

***r*-1-*tert*-Butyl-*c*-4-cyano-*c*-3-phenylsulfonylcyclohexane** (20).—The *r*-1,*c*-3,*c*-4 nitrile phenyl sulfide (**14**, 1.2 g) was oxidized with H_2O_2 in H_2SO_4 as usual to give the **nitrile sulfone** (0.654 g, 53%): mp 138.5–139.5°; ir (KBr) 2250 (C≡N), 1351, 1155 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 7.80, 7.50 (m, 5 H, Ar H), 3.22 (br s, 1 H, C_4 H), 2.96 (d of t, J_{aa} = 13, J_{ae} = 4 Hz, 1 H, C_3 H), 0.82 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{17}H_{23}NO_2S$: C, 66.64; H, 7.89. Found: C, 66.47; H, 7.84.

Base-Catalyzed Equilibration of the *r*-1,*t*-3,*t*-4 Sulfone Phthalimide (7).—A solution of sulfone phthalimide (**7**, 300 mg) in absolute ethanol containing sodium ethoxide (from 50 mg of Na) was boiled under reflux for 24 hr. The solvent was evaporated and the residue treated with phthalic anhydride (0.25 g) in acetic acid (15 ml) and boiled for 4 hr. The solvent was evaporated and the residue recrystallized from ethanol–pentane and then from ethanol to give a near-quantitative yield of the ***r*-1-*tert*-butyl-*c*-3-phenylsulfonyl-*t*-4-phthalimidomethylcyclohexane** (**8**), mp 142–143°, depressed on admixture with starting **7**.

Anal. Calcd for $C_{25}H_{29}NO_4S$: C, 68.31; H, 6.65; H, 3.18. Found: C, 68.26; H, 6.47; H, 3.30.

Equilibration of *r*-1,*t*-3,*t*-4 Sulfone Amine.—The equilibration was carried out as for **7** above to give an oil which was converted into the phthalimide (**8**), mp 142–143°, undepressed on admixture with a sample obtained as above.

Equilibration of *r*-1,*t*-3,*c*-4 (12) and *r*-1,*c*-3,*c*-4 (13) Sulfone Phthalimides.—One of the sulfone phthalimides (0.20 g) was added to a solution of sodium (50 mg) in ethylene glycol (5 ml) and the solution heated at 130 ± 2° for varying lengths of time (24 to 192 hr). The solution was then poured into water (60 ml), sodium chloride (1 g) added, and the solution continuously extracted with $CHCl_3$ for 24 hr. The $CHCl_3$ was evaporated, the residue was dissolved in benzene (30 ml), phthalic anhydride (100 mg) and triethylamine (5 drops) were added, and the mixture was boiled under reflux using a Dean-Stark separator for 15 hr. It was then washed with 1 *N* HCl (2 × 15 ml) and brine (2 × 15 ml), dried ($MgSO_4$), and evaporated. The residue (100 mg) was dissolved in deuteriochloroform and analyzed by nmr. Relative amounts of the two sulfone phthalimides were determined by integration of the two *tert*-butyl peaks using a 50-Hz sweep width. The *tert*-butyl group of the *r*-1,*t*-3,*c*-4 isomer absorbed at δ 0.91, while that of the *r*-1,*c*-3,*c*-4 isomer absorbed at 0.93 and the lines were well resolved on the 100-MHz instrument. The isomers were isolated by preparative tlc (1-mm plates, 60% benzene, 39% $CHCl_3$, 1% NH_3 eluent). Only two products were detected, namely, **12** and **13** (R_f 0.50 and 0.44, respectively). Starting from either **12** or **13**, the ratio found was 60:40 **12**:**13**. Equilibrium was attained after 24 hr, and further heating had little effect on the isomer ratio.

When **12** was boiled with MeONa in MeOH or EtONa in EtOH for prolonged periods of time the starting sulfone phthalimide was recovered quantitatively.

Attempted Equilibration of the *r*-1,*c*-3,*c*-4 Nitrile Sulfide (14).—The nitrile (**14**, 0.14 g) in absolute methanol (10 ml) was treated with NaOMe (54 mg) and the solution was boiled under reflux for 3 days and kept at room temperature for 10 days. Work-up followed by glc analysis indicated only the presence of starting material.

The nitrile (0.14 g), NaOMe (54 mg), and thiophenol (5 drops) in dimethylformamide (5 ml) were heated in a sealed tube at 110° for 15 days. Glc analysis showed that starting material was unchanged.

Addition of Hydrogen Chloride to 4-*tert*-Butyl-1-cyanocyclohexene.—4-*tert*-Butyl-1-cyanocyclohexene (2 g) was dissolved in dry ether (10 ml) and anhydrous HCl was bubbled through for 2 hr. The solution was kept at room temperature overnight, the solvent evaporated, and the residue dissolved in petroleum ether (bp 30–60°). ***r*-1-*tert*-Butyl-*t*-3-chloro-*t*-4-cyanocyclohexane** (0.69 g, 37%), mp 50–52°, separated: ir (KBr) 2970, 2900, 2870, 2230 (C≡N), 685 cm^{-1} (CCl); nmr (CCl_4) δ 4.60 (br s, 1 H, C_3 H), 2.85 (d of t, J_{aa} = 7.5, J_{ae} = 2.5 Hz, C_4 H), 0.82 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{11}H_{18}ClN$: C, 66.15; H, 9.08. Found: C, 66.20; H, 9.28.

Reaction of Chloro Nitrile 22 with Thiophenoxide Ion.—Thiophenol (1.10 ml) and the chloro nitrile (1 g) were added to a solution of sodium (0.23 g) in ethanol (20 ml), and the solution was then stirred at room temperature for 24 hr. Acidification with glacial acetic acid was followed by removal of thiophenol, extraction of the product, and glc analysis on a 20% SE-30 on Chromosorb W (60–100 mesh) 6 ft × $^3/_{16}$ in. column at 245°. 4-*t*-Butyl-1-cyanocyclohexene was detected together with traces of **2** and **3**. Column chromatography on silica gel (50 g) and elution with benzene–petroleum ether (1:4 v/v) gave the olefin (0.30 g, 60%) and diphenyl disulfide (0.45 g).

Similar results were obtained when aqueous ethanol or DMSO were used as the solvents.

Attempted Hydrolysis of 3.—Thiophenoxy nitrile **3** (5 g) was boiled under reflux with 6 *N* HCl (50 ml) for 48 hr and for 6 days, but it was recovered unchanged in each case.

Attempted Deamination of *r*-1-*tert*-Butyl-*t*-3-phenylsulfonylcyclohexane-*t*-4-carboxylic Acid Amide (4).—Sodium nitrite (5 g) was added in small portions to a cold (0°) solution of the amide (3 g) in glacial acetic acid (50 ml). The mixture was allowed to come to room temperature, the acid was evaporated on a film evaporator to give an oil which was poured into water and extracted with ether, and the ether layer was washed with $NaHCO_3$ solution. The ether was dried ($MgSO_4$) and evaporated to yield the starting amide, mp 170–173°.

When the amide was heated with amyl nitrite only a dark tar could be isolated.

Attempted Addition of Hydrogen Bromide to 1.—The olefin (0.815 g) in glacial acetic acid (10 ml) was treated with 47% HBr (3 ml) and the solution stirred at room temperature overnight. It was poured into water (25 ml), basified, and extracted with ether (3 × 25 ml). The dried ($MgSO_4$) ether extracts were evaporated to give **4-*tert*-butylcyclohexene-1-carboxamide** (0.5 g, 55%): mp 178–179°; ir (KBr) 3490, 3350, 3310, 1685, 1650 cm^{-1}; nmr ($CDCl_3$) δ 6.71 (br s, 1 H, vinyl H), 6.10 (br s, 2 H, $CONH_2$), 0.88 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56. Found: C, 73.08; H, 10.70.

Registry No.—**1**, 7370-14-1; **2**, 23191-40-4; **3**, 35905-86-3; **4**, 35905-87-4; **5**, 35905-88-5; **6**, 35905-89-6; **7**, 35905-90-9; **8**, 35905-91-0; **9**, 35905-92-1; **10**, 35905-93-2; **11**, 35905-94-3; **13**, 35905-95-4; **14**, 35905-96-5; **15**, 35905-97-6; **16**, 35905-98-7; **20**, 35905-99-8; **22**, 35906-00-4; thiophenol, 108-98-5; hydrogen chloride, 7647-01-0; *r*-1-*tert*-butyl-*t*-4-cyano-*t*-3-phenylsulfonylcyclohexane, 35906-01-5; *r*-1-*tert*-butyl-*t*-4-aminomethyl-*t*-

3-phenylsulfonyl cyclohexane, 35925-50-9; 4-*tert*-butylcyclohexene-1-carboxamide, 35906-02-6.

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The Direct Acylation of Pyridine 1-Oxides

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The reaction of pyridine 1-oxides with BuLi at low temperature in nonprotic solvents gives the 2-lithiopyridine 1-oxides, which react with carbon dioxide to give acids and with esters to give ketones. Some interesting by-products are obtained when *N*,*N*-dimethylacetamide and benzonitrile are used as the electrophiles.

Though the direct introduction of an acyl group into the pyridine nucleus is possible *via* the Emmert reaction (a nucleophilic attack at the α positions[1]), the direct electrophilic acylation of pyridine derivatives has not been feasible until recently, since these π-deficient rings do not undergo the Friedel–Crafts reaction. In an earlier paper, we reported the base-catalyzed deprotonation of pyridine 1-oxides in nonprotic solvents and the trapping of the carbanion so formed with aldehydes and ketones to give 2- and 2,6-dialkylated pyridine 1-oxides.[2] We now report the reaction of these 1-oxido-2-pyridyllithium derivatives with carbon dioxide, esters, amides, and nitriles to give acids and ketones.[3]

The 2-pyridyl 1-oxide anions were generated by the addition of *n*-butyllithium to a solution of the *N*-oxide in ether or tetrahydrofuran at −65°, and trapped by the addition of the electrophile. The results of the carboxylation of the anions are summarized in Table I.

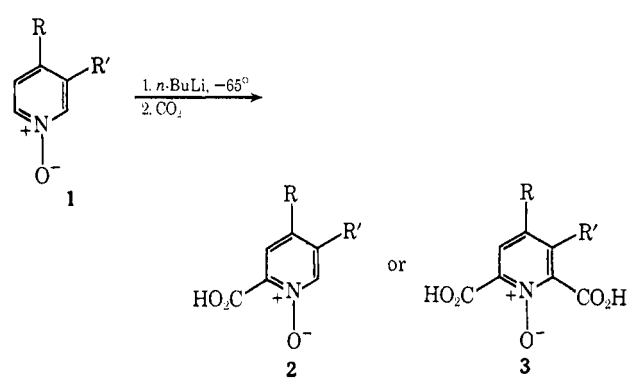
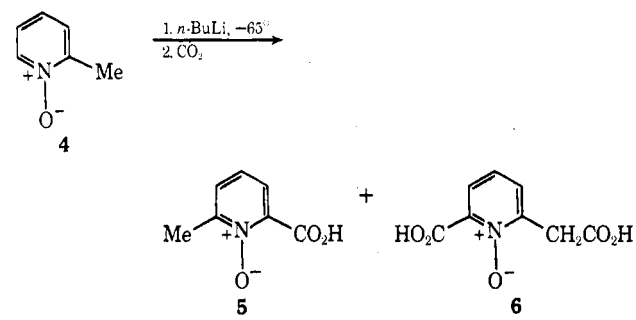


TABLE I

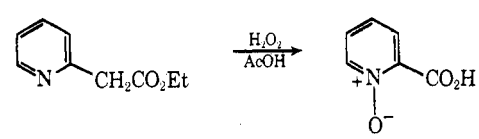
CARBOXYLATION OF 1-OXIDO-2-PYRIDYLLITHIUM DERIVATIVES (1)

1	Product (%)	Registry no.
R = Cl; R′ = H	2 (49.0)	35895-54-6
R = Me; R′ = H	3 (48.0)	35895-55-7
R = Cl; R′ = Me	2 (23.8)	17117-05-4
R = R′ = Me	2 (17.9)	35895-57-9

Authentic **2** (R = Cl; R′ = Me) was synthesized by nitration of 5-methylpicolinic acid 1-oxide to yield the nitro compound, followed by treatment with acetyl chloride. As before,[2] a 3-methyl substituent directs deprotonation preferentially para to itself. Only one example of 2,6 dilithiation was observed here, and that in the case of 4-picoline 1-oxide. Methyl groups at C_3 or C_4 are not affected. On the other hand, as observed previously in the alkylation reactions, a 2-methyl substituent does undergo some deprotonation as well. Thus, when 2-picoline 1-oxide (**4**) was lithiated and then treated with CO_2, both 6-methyl-2-picoline 1-oxide (**5**) and 2-picoline-6,α-dicarboxylic acid 1-oxide (**6**) were obtained.



For possible comparison with **5** an attempt was made to synthesize authentic 2-pyridylacetic acid 1-oxide from **4** *via* the ethyl pyruvate as reported by Adams and Miyano[4] or by oxidation of ethyl 2-pyridylacetate with 30% H_2O_2 in glacial acetic acid. In both cases, picolinic acid 1-oxide was the final product obtained instead of the desired acetate.



6-(1-Hydroxycyclohexyl)-3,4-dimethylpyridine 1-oxide (**7**) could only be metalated and carbonated in very low yield to give **8**, the main product formed apparently being that of addition of butyllithium to the azomethine linkage (**9**).

Various carbonyl compounds were used to effect the acylation of the 2-lithio 1-oxides, and esters were found to give the best results, though yields of ketones were generally low. Reaction of 3,4-lutidine 1-oxide with *n*-butyllithium followed by ethyl acetate and work-

(1) R. A. Abramovitch and A. R. Vinutha, *J. Chem. Soc. C*, 2104 (1969).

(2) R. A. Abramovitch, E. M. Smith, E. E. Knaus, and M. Saha, *J. Org. Chem.*, **37**, 1690 (1972).

(3) Preliminary communication: R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Amer. Chem. Soc.*, **89**, 1537 (1967).

(4) R. Adams and S. Miyano, *ibid.*, **76**, 3168 (1954).