3 H, J = 7 Hz), 3.26 (d, 1 H, J = 8 Hz), 3.60 (s, 3 H), 417 (q, 2 H, J = 7 Hz), 5.55 (m, 2 H), 6.3 (m, 3 H); mass spectrum, m/e 194 (11), 121 (100), 91 (28), 78 (15), 77 (15).

Ethyl 2-Methoxy-1,4,6-cycloheptatriene-1-carboxylate (10): trace; IR 2990, 1717, 1640, 1270 cm^{-1}; NMR δ 1.31 (t, 3 H, J = 7 Hz), 2.67 (d, 2 H, J = 7 Hz), 3.70 (s, 3 H), 4.23 (q, 2 H, J = 7 Hz), 5.37 (dt, 1 H, J = 7, 9 Hz), 6.00 (dd, 1 H, J = 2, 7 Hz), 6.19 (dd, 1 H, J = 7, 9 Hz), 7.07 (d, 1 H, J = 2 Hz); mass spectrum, m/e 194 (19), 165 (77), 149 (19), 148 (23), 121 (100), 120 (32), 91 (33), 78 (23), 77 (34).

Ethyl 2-Phenoxypropanoate (11): trace; IR 2970, 2940, 1760, 1730, 1605, 1595, 1500, 1290, 1250, 755, 690 cm^{-1}; NMR δ 1.30 (t, 3 H, J = 7 Hz), 1.60 (d, 2 H, J = 7 Hz), 4.30 (q, 2 H, J = 7 Hz), 4.73 (q, 1 H, J = 7 Hz), 6.70–7.40 (m, 5 H); mass spectrum, m/e 194 (20), 121 (100), 94 (24), 93 (11), 77 (39).

4-(Carboethoxy)-2,4,6-cycloheptatrienone (1). *N*-Bromosuccinimide (0.85 g, 0.0048 mol) and benzoyl peroxide (ca. 5 mg) were added to a solution of 0.70 g (0.0036 mol) of triene **4** in 25 mL of CCl_4. Nitrogen was slowly bubbled through this refluxing solution for 1 h. After the solution was cooled under nitrogen, the mixture was treated with solid sodium bicarbonate. This heterogeneous mixture was stirred for 15 min and the solid removed by filtration. Evaporation of the solvent left a brown oil which was immediately filtered through silica gel (hexanes–ethyl acetate, 1:1).[19] Removal of solvent yielded 0.57 g (88%) of **2** as brownish crystals: UV (EtOH) 233 nm (ϵ 17 000), 305 (ϵ 4200), 315 (ϵ 4200); IR 2990, 1720, 1640, 1595, 1270, 1220 cm^{-1}; NMR δ 1.40 (t, 3 H, J = 7 Hz), 4.40 (q, 2 H, J = 7 Hz), 6.95–7.35 (m, 3 H), 7.70–8.05 (m, 2 H); ^{13}C NMR δ 13.9, 62.1, 134.2, 134.6, 135.5, 137.6, 140.9, 145.1, 165.4, 187.3; mass spectrum, m/e 178, 150, 149, 133, 122, 105 (100).

3-(Carboethoxy)-2,4,6-cycloheptatrienone (2). By use of the method described for **1** above, 3-(carboethoxy)tropone (**2**) was obtained from **7** in 90% yield:[19] UV (EtOH) 216 nm (ϵ 9900), 228 (sh, ϵ 9600), 310 (ϵ 2500), and 325 (sh, ϵ 2300); IR (film) 2990, 1720, 1640, 1250 cm^{-1}; NMR δ 1.40 (t, 3 H, J = 7 Hz), 4.40 (q, 2 H, J = 7 Hz), 6.95–8.00 (m, 5 H); ^{13}C NMR δ 14.1, 62.6, 133.5, 133.8, 136.9, 137.0, 142.4, 143.6, 166.8, 187.4; mass spectrum, m/e 178, 150, 149, 133, 105 (100).

Acknowledgment. We are grateful to PRF Grant No. 9658 G and the UCSD Academic Senate for support of this work. Recently NIH Shared Instrument Program Grant GM 27583 permitted purchase of a mass spectrometer used in much of this project.

Registry No. **1**, 80865-79-8; **2**, 80865-80-1; **3**, 2555-49-9; **4**, 60058-37-9; **7**, 41585-58-4; **8**, 41585-61-9; **9**, 80865-81-2; **10**, 80865-82-3; **11**, 42412-84-0; **12**, 17606-97-2.

(19) These compounds were stable for days in dilute benzene solution under N_2 at 0 °C. They could not be distilled by use of a Kugelrohr apparatus without complete decomposition. Storage as neat compounds led to complete decomposition within 48 h. In all instances, these products appeared to be polymeric.

Thermodynamic and Kinetic Aspects of Tropinone Oxide

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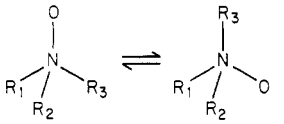
To the best of our knowledge no reaction leading to the racemization (or epimerization) of a tetracoordinated N atom of an amine oxide is known. Such a process could possibly provide an insight into the nature of the nonbonded interactions of the oxygen atom and enable the evaluation of various thermodynamic parameters. Previously we have evaluated such parameters in the 1-methylpiperidine 1-oxide system using the average chemical shift method.[1]

Table I. Diastereomeric Distribution of Tropinone Oxide

reaction method	% composition 1 (δ 3.42)	% composition 2 (δ 3.65)
A	90	10
B	60	40
C	40	60

We have ascertained that oxidation of amines to amine oxides is a kinetically controlled reaction.[1] Various attempts to induce equilibration of amine oxides (eq 1) have



(1)

failed. Such attempts were based on bond breaking and making reactions involving the N–O linkage. In fact, our discovery of the reactivity of amine oxides toward organometallic carbonyl complexes,[2] which turned out to be a widely accepted method for the mild oxidation (disengagement) of such comlexes, evolved from such futile attempts.

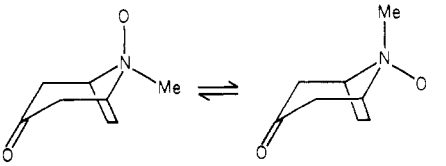
Consequently, we have turned to a different approach which involves the reversible N–R rather than N–O bond cleavage, which indeed turned out to be a successful one. This approach has two basic requirements: (a) activation of the N–R (R = alkyl) bond toward a reversible bond breaking and making process; (b) The availability of an appropriate molecular system which will enable the experimental detection of the equilibrating species.

It turned out that tropinone-1-oxide is an ideal system for such a study.

Tropinone 1-oxide was prepared by the foollowing three methods at 25 °C: (a) oxidation of tropinone with H_2O_2(aq) in acetone; (b) cycloaddition of *N*-methylhydroxylamine to 2,6-cycloheptadienone; (c) oxidation of tropinone with *m*-chloroperbenzoic acid in CH_2Cl_2.

In each case the final reaction mixture was examined by NMR. Invariably two N–Me signals at δ 3.42 and 3.65 were observed. Their relative intensities were dependent on the method of preparation (Table I).

Next, it was necessary to correlate the NMR signals of the N–Me group with the configurations of the diastereomeric tropinone oxides. For this purpose we have separated and purified the two components and converted them to the picrates. Kashman et al.,[3] using method B, obtained the two isomeric tropinone oxides **1** and **2** (eq 2).



(2)

1 2

They were characterized on the basis of the infra red spectrum of **1** (picrate) which lacks the C=O stretching band. It was argued that only **1** may interact to give **3**[3,4] (eq 3).

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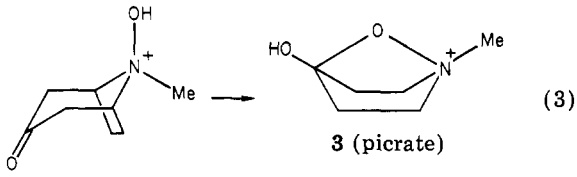


1 (picrate) 3 (picrate) (3)

In our experiment, the picrate of the major isomer of reaction by method A lacked the carbonyl band in the infrared spectrum. Therefore, we can now correlate the NMR signal at δ 3.42 with 1 and that of δ 3.65 with 2 (Table I). The relative chemical shift of the N–Me signals of the isomeric tropinone oxides is in agreement with that found by Kashman;[3] however, it is reversed with respect to tropine 1-oxide[4] and 1-methylpiperidine 1-oxide.[1]

Having secured the configurational and NMR assignments, we can now turn to the kinetic and thermodynamic aspects of the system. We have found that heating of the amine oxides in organic solvent or, better, placing the picrates, either of the pure isomers or of the isomeric mixtures, in contact with basic alumina (activity III) at 25 °C invariably leads to a mixture of 1 and 2 (Scheme I) with a distribution ratio of 9:1, respectively. Therefore, the above composition represents an equilibrium concentration of the isomeric tropinone oxides at 25 °C.

Although not rigorously proved, the equilibration occurs most probably via a reversible Michael reaction which is catalyzed very efficiently by basic alumina.

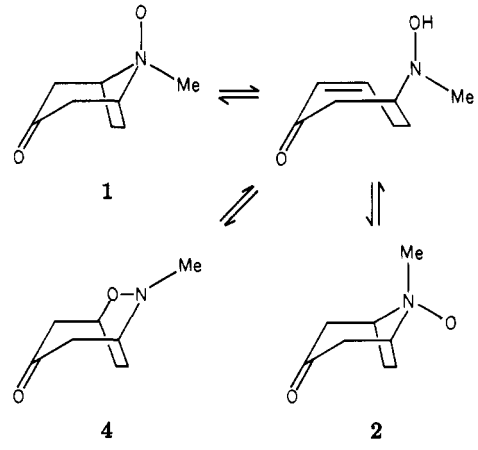
It has been observed that the picrates (in the absence of alumina) are configurationally more stable than the free amine oxides and hardly equilibrate in organic solvents or even in water solution. We believe that the protonated amine oxide (picrate) prevents the abstraction of the proton α to the carbonyl, the step essential for the reverse Michael reaction.

Compound 4 is isomeric with tropinone oxide and can be formed kinetically in the equilibration process. Nevertheless, it has not been detected as a stable product. Its absence, in spite of the fact that a C–O bond (74 kcal/mol) is substantially stronger than a C–N bond (53 kcal/mol), implies that the N–O bond in 4 (48 kcal/mol) is substantially weaker than that in 1 (or 2), for which we could not find a reliable bond energy value. It is inconceivable that either 1 or 2 actually possesses structure 4 since kinetically controlled oxidation (vide infra) of tropinone, where 4 cannot be formed, generates the same isomeric pair which is obtained by equilibration.

Turning now to Table I, the reaction by method A is clearly thermodynamically controlled. The reaction by method B is either kinetically controlled or partially equilibrated. However, we argue that reaction by method C is purely kinetically controlled since a very similar selectivity (75% equatorial oxidation, 25% axial oxidation) was obtained in the oxidation of tropine.[5] Also, oxidation of *cis*-1,2,6-trimethylpiperidine,[6] a reasonable model for tropinone (alkylated at the 2- and 6-positions) yields a 61:39 equatorial/axial mixture of oxidation products. Obviously in neither of the above two systems can equilibration take place by the postulated mechanism.

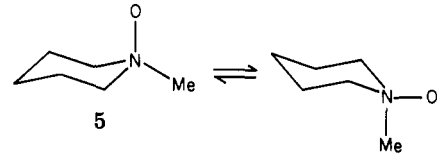
It should be noted that reaction by method C was carried out in the presence of acid. Recalling the configurational stability of the picrates of tropinone oxides, we

Scheme I



suggest an identical protection mechanism of the α-protons under the acidic conditions of method C, thus leading to kinetically controlled oxidation.

From the equilibration data it follows that K_1 = [2]/[1] = 1/9; $\Delta G°_{298}$ = 1.3 kcal/mol. From previous studies[1] we have found that K_2 = [6]/[5] = 0.62; $\Delta G°_{298}$ =0.28 kcal/



5 6 (4)

mol, in the same solvent. This latter value which represents the differential interaction of the Me group and the oxygen atom with C-3 and C-5 indicates that the Me group has larger steric requirements than the oxygen atom. Similar interactions must also prevail in the tropinone system (1 ⇌ 2) but are now opposed by the nonbonded interactions generated by the 2,6-ethylene bridge. Thus regardless of the magnitude of the latter interaction we have anticipated a shift in the equilibrium toward 2 (1 ⇌ 2) with respect to 5 ⇌ 6. Experimentally, however, the equilibrium was shifted toward 1. The origin of the difference $\Delta G°_{1,2} - \Delta G°_{5,6}$ = 1 kcal/mol may lie in the transannular interaction similar to that which is described by 3. The lowering of the C=O stretching frequency of 1 (1710 cm^{-1}) compared to that of 2 (1720 cm^{-1}) may support such a dipol–dipol interaction: N—O→C=O. Of course the energy scheme is more complex since the ring system is now in a boat rather than a chair conformation. Nevertheless, the overall effect must be that of stabilization.

From Table I it is clear that the kinetically favored isomer of tropinone 1-oxide (2) is the thermodynamically less stable one. It is formed by an equatorial approach of the oxidant (60%). Very similar selectivities were obtained in the kinetically controlled oxidation reactions of tropine (75%)[5] and *cis*-1,2,6-trimethylpiperidine (61%).[6] It may therefore be concluded that the previously proposed 1,4-transannular dipole–dipole interaction is favored in the ground state but not in the oxidation transition state. This may explain the above kinetic vs. thermodynamic stability of 2.

It is noteworthy that the axial approach of the oxidant in the kinetically controlled oxidation of 4-*tert*-butyl-1-methylpiperidine (95%)[1] and 1,4-bis(*tert*-butyl)piperidine (100%)[6] is favored over the equatorial approach. Thus, alkyl substituents at the 2- and 6-positions of the piperidine ring invert the selectivity of the oxidation reaction.

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(6) Kawazoe, Y.; Tsuda, M. *Chem. Pharm. Bull.* **1967**, *15*, 1405.
(7) Shvo, Y.; Kaufman, E. D. *J. Org. Chem.*, in press.

Experimental Section

Preparations of Tropinone 1-Oxide. Method A. A solution of tropinone (1.4 g, 0.01 mol), H_2O_2 (1.5 mL 30% aqueous solution) in acetone (50 mL) was kept at 25 °C for 48 h. The solution was dried with K_2CO_3 and concentrated in vacuo, and a solid precipitated (1.3 g, 89%) upon addition of CCl_4. It was found to be a mixture of **1** and **2** (9:1). Crystallization from acetone–petroleum ether gave pure **1**: mp 100 °C; NMR ($CDCl_3$) δ 2–2.5 (m, 6 H), 3.42 (s, 3 H), 3.5–4.0 (m, 4 H); IR (Nujol) 1710 cm^{-1}; picrate, mp 210 °C; IR (KBr) no carbonyl abssorption band. Anal. Calcd for $C_{14}H_{16}N_4O_9$; C, 43.76; H, 4.20; N, 14.58. Found: C, 43.96; H, 4.32; N, 14.66.

By use of thick layer chromatography (Neutral Alumina) with chloroform–methanol (9:1) **2** was obtained: mp 100 °C (acetone–petroleum ether); NMR δ ($CDCl_3$) 1.9–2.5 (m, 6 H), 2.5–3.0 (m 2 H), 3.65 (s, 3 H), 3.6–4.1 (2 H); IR (Nujol) 1720 cm^{-1}; picrate, mp 214 °C; IR (KBr) 1740 cm^{-1}.

Method B. The procedure of Kashman et al.[3] wtih 1.08 g of 2,6-cycloheptadienone was followed. The reaction mixture was filtered and pcric acid (ethanol) was added; 2.6 g (77%) of a mixture of the picrates of **1** and **2** (40:60) was obtained.

Method C. A solution of tropinone (1.4 g) and *m*-chloroperbenzoic acid (3.0 g) in CH_2Cl_2 (50 mL) was kept at 25 °C for 72 h. Addition of picric acid (ethanol) gave a solid (3.59 g, 93%) which was found to be a mixture of the picrates of **1** and **2** (40:60).

Equilibration Experiments. The picrate of **2** (0.5 g) in acetone (20 mL) was loaded on a column of basic alumina (III). A chloroform methanol mixture (9:1) eluted the free amine oxide. The solution was concentrated at room temperature to a volume of 20 mL. A saturated solution of picric acid in $CHCl_3$ was added. There was obtaineg 0.45 g (90%) of a mixture of the picrates of **1** and **2** in a ratio of 9:1, respectively (NMR).

The same procedure was followed by using the mixture of the picrates obtained by method C. The distribution of the amine oxides was identical with that of the previous experiment.

Registry No. **1**, 54807-25-9; **1** picrate, 54807-27-1; **2**, 54807-26-0; **2** picrate, 54807-28-2.

Reaction of Dimethyl Acetylenedicarboxylate with 2-Ethyl-3-phenyl-2*H*-5,6-dihydro-1,2-oxazine

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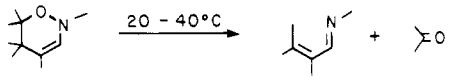
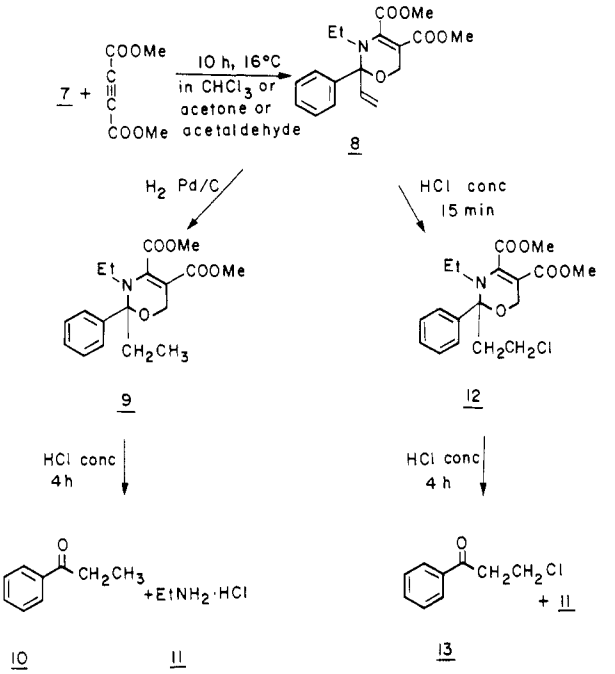
2-Alkyl-2*H*-5,6-dihydro-1,2-oxazine derivatives **1** have been shown by Eschenmoser to undergo a clean cleavage to α,β-unsaturated imines **2** and aldehydes or ketones **3**.[1]



1 **2** **3**

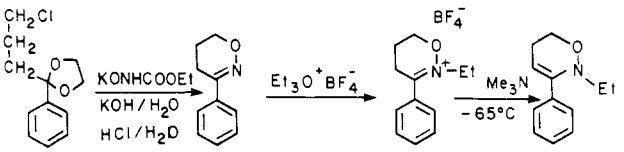
The basis for the ease of this clean decomposition is not completely clear, with repulsion between the higher nuclear charges and/or nonbonded electron pairs considered as responsible.[1] Although this process found use in the synthesis of medium-ring lactones[2] and pyridine derivatives,[3] little work has been published on other reactions of this system.[4]

Scheme I



As part of our research on the synthetic uses of 1,2-oxazines, we examined the reaction of 2-ethyl-3-phenyl-5,6-dihydro-1,2-2*H*,4*H*-oxazine (**7**) with dimethyl acetylenedicarboxylate (DMAD).

The starting cyclic oxime ether **5** was obtained from 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane (**4**), in analogy



4 **5** **6** **7**

to the preparation of 3-methyl-4*H*-5,6-dihydro-1,2-oxazine described by Brandman and Conley.[5] N-Ethylation with $Et_3O^+BF_4^-$ in CH_2Cl_2 gave the oxoimminium salt **6** in 87% yield. Reaction of **6** with 1 equiv Me_3N in $CHCl_3$ for 1 min at −65 °C gave a quantitative yield of **7** isolated as an oily liquid.

A mixture of **7** and DMAD in chloroform, acetone, or acetaldehyde solutions after 10 h at 16 °C gives, after workup and separation, an adduct in 50–75% yield. Analytical data are consistent with a 1:1 adduct ($C_{18}H_{21}NO_5$), and the spectral data indicate structure **8** (Scheme I). The ^1H NMR spectrum shows a vinylic ABX proton system indicating a monosubstituted ethylene moiety. The ^{13}C NMR spectrum is also in good accord with the structure **8**.

The following degradation reactions prove structure **8**. Hydrogenation with 1 equiv of H_2 affords **9**. Acid hydrolysis of **9** for 4 h affords 1-phenyl-1-propanone (**10**) and $EtNH_3^+Cl^-$ (**11**). Similarly, acid hydrolysis of **8** gave **11** and the β-chloro ketone **12**. The final proof for the structure of **8** was given by X-ray crystallography. The overall molecular structure is shown in Figure 1; detailed geometry data are given in Table I (supplementary material). The overall shape of the 2,3,5,6-tetrahydro-1,3-

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