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Bicyclic Bases (1,2). Ambident Anions as Intramolecular Nucleophiles in the Formation of 2-Oxa-5-azabicyclo[2.2.1]heptane Derivatives

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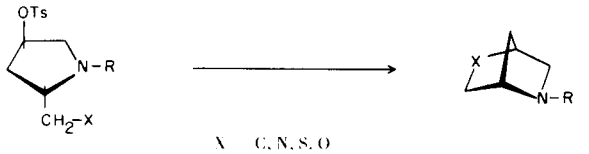
The intramolecular cyclization of the ambident anion **5** derived from condensation of *N,O*-ditosylhydroxy-L-proline acid chloride with dimethyl malonate anion was studied under a variety of reaction conditions. Cyclization occurred solely by *O*-alkylation to give 2-oxa-5-azabicyclo[2.2.1]heptanes. The NMR spectra of the bicyclo compounds are discussed.

We have reported (2-5) that properly substituted hydroxy-L-proline derivatives (**1**) may be internally cyclized to azabicyclo[2.2.1]heptane ring systems (**2**) containing different endocyclic heteroatoms. In connection with work related to the further exploration of this synthetic



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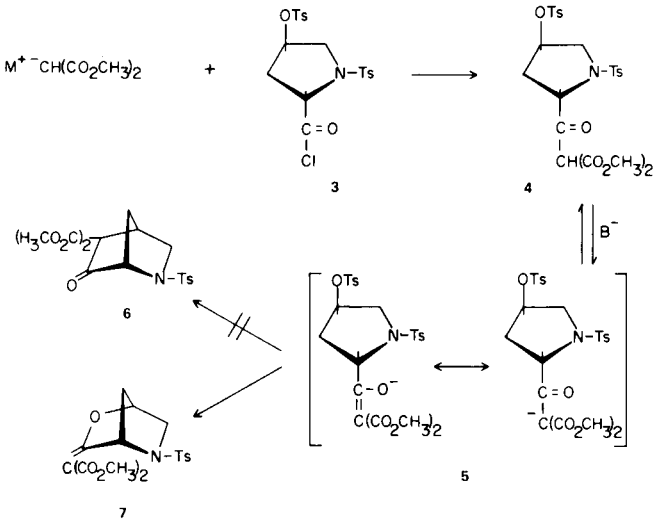
route, we have investigated the special case where the internal nucleophile is an "ambident anion" (6).



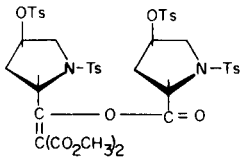
It was anticipated that bicyclic ring system **6** could be prepared by cyclization of intermediate **4** derived from the condensation of acid chloride **3** with dimethylmalonate anion. However, since anion **5** is an ambident anion (possessing two different reactive positions), the internal cyclization can occur either by intramolecular *O*- or *C*-alkylation.

The acid chloride **3** was prepared from either the sodium or lithium salt of *N,O*-ditosylhydroxy-L-proline (3) utilizing oxalyl chloride (7). The acid chloride was not isolated nor further purified. However its presence could be demonstrated by the nearly quantitative recovery of methyl ester **10** when treated with anhydrous methanol.

Since enolate anion **5** should be a weaker base than dimethylmalonate anion, it was anticipated that cyclization might occur during the preparation of **4**. Consequently when the reaction was carried out in aprotic solvents such as benzene or tetrahydrofuran, intermediate **4** was allowed to react *in situ* with excess dimethylmalonate anion. The only product isolated under these reaction conditions possessed spectral characteristics that were consistent with vinyl ether **7** rather than bicyclic ketone **6**. The infrared spectrum of **7** showed a strong absorption at 1625 cm^{-1}, characteristic of a vinyl ether (8). The UV spectrum exhibited two strong absorptions at 231 mμ (ϵ = 20,000) and 250 mμ (ϵ = 15,000). The 250 mμ absorption correlates well with that calculated (9) for an α,β-unsaturated ester in which the double bond is exocyclic and fully substituted. 2-Methyl-3-carbethoxy-5,6-dihydro-4*H*-pyran exhibits a similar absorption (10).

Finally, the NMR spectrum of **7** clearly shows the presence of the 2-oxa-5-azabicyclo[2.2.1]heptane skeleton (Table I).

When the same reaction was carried out using equivalent amounts of **3** and malonate anion, an additional product **8** was obtained in minor quantity. This uncyclized vinyl ester **8** apparently arises from exclusive reaction at the oxygen of the ambident anion **5** with acid chloride **3**.



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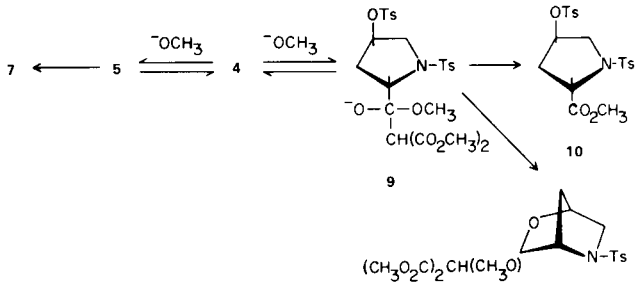
Taylor and McKillop (11,12) have reported that the thallium salts of β-keto esters can be manipulated to give either exclusive *C*- or *O*-alkylation. When the thallium salt of dimethylmalonate reacted with **3** in several aprotic solvents the only product found was the bicyclic vinyl ether **7**. There was no evidence of any *C*-alkylation products.

It is well documented (13-15) that *C*-alkylation of an ambident anion is favored by hydroxylic solvents whereas, aprotic solvents favor *O*-alkylation. We therefore carried out the cyclization of **4** in methanol. This procedure required the preliminary isolation of the intermediate **4**, since the acid chloride **3** is rapdily esterified in methanol. This was easily accomplished by reacting **3** with excess sodio dimethylmalonate in tetrahydrofuran and quenching the reaction with 30-45 seconds. Within this time all the acid chloride was consumed and the amount of cyclization was minimal. Attempts at purification of **4** were unsuccessful and consequently all subsequent reactions were carried out on the crude product.

When the intermediate **4** was reacted with sodium methoxide in methanol, three products were isolated. Of these, the major components were the bicyclic vinyl ether **7** and methyl ester **10**. A small amount of a new compound also was obtained whose NMR spectrum was characteristic of the 2-oxa-5-azabicyclo[2.2.1]heptane system (Table I). Additionally, the spectrum showed three sharp singlets at 3.33, 3.79 and 4.28 ppm, integrating for three, six and one protons respectively. The signal at 3.79 ppm was assigned to the two ester methyl groups. The singlet at 3.33 ppm is consistent with a methyl ether, and the sharp singlet at 4.28 ppm, being nonexchangeable with deuterium oxide, is assigned to the α-proton of the malonate moiety. This data best fits the cyclic ketal structure **11**. As final proof, the ketal was converted to the vinyl ether **7** using methoxide.



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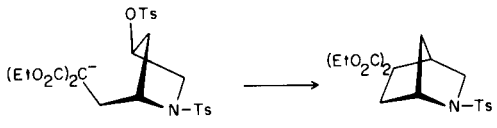
It is noteworthy that **7** is not the precursor of **11**, nor is **11** an artifact of the workup procedure. This was demonstrated by the failure to generate ketal **11** from **7** using either methanolic methoxide or methanolic hydrochloric acid. Apparently the incorporation of methanol must occur prior to cyclization. A reasonable pathway by which both the ketal **11** and methyl ester **10** can arise is through intermediate **9** which can cleave to form **10** or cyclize to form **11**.

The base-catalyzed cyclization of **4** in methanol was conducted under a variety of conditions. The sodium, magnesium, and thallium salts of dimethylmalonate anion were used as the source of base and the reaction temperatures were varied. Under all conditions only the three previously mentioned products were found and there was no evidence for *C*-alkylation. However, there were some striking variations in the distribution of these products under certain reaction conditions. When the cyclization was carried out in methanol at room temperature using sodio dimethylmalonate as base, the major products isolated were the two bicyclic *O*-alkylation products **7** and **11**. Very little methyl ester **10** could be detected. However, when the same reaction was conducted at 0° the methyl ester was overwhelmingly the predominant product and only trace amounts of the other two compounds were observed. When magnesio dimethylmalonate was used as the base catalyst, reaction took place only at elevated temperature. Under these conditions no methyl ester was detected and only the two cyclization products were formed.

It is not unreasonable to conclude that the lack of *C*-alkylation is a consequence of unfavorable steric hinderance in the transition state for cyclization. Cyclization to yield bicyclic ketone **6** requires displacement of a secondary tosyl group by a sterically crowded tertiary carbanion.



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The possibility that such a displacement can occur has recently been demonstrated by the successful cyclization of **12** to **13** (16). However this reaction requires considerably more vigorous conditions than cyclization of the ambident anion **5**. This reaction demonstrates that when no alternative pathways (*i.e.* *O*-alkylation or cleavage) are possible *C*-alkylation will occur.

The various 2-oxa-5-azabicyclo[2.2.1]heptanes which result from intramolecular *O*-alkylation all have characteristic NMR spectra for the ring protons. Table I lists the chemical shifts of the ring protons for several of these bicyclic ethers. The bridgehead protons H_1 and H_4 invariably appear at lowest field by virtue of their proximity to the heteroatoms. The exact assignment of these two signals, however could not be made soley on the basis of chemical shifts. Spin-decoupling experiments unambigously differentiated H_1 from H_4, since only H_1 is able to couple with the *exo* methylene proton at C_6 (5).

The methylene protons at C_6 characteristically appear between 3 and 4 ppm and comprise the AB portion of an ABX spin system in which Jax ~ 0 (2,3,5). In bicyclic ethers (**7**, **11**, **15**) H_{6a} and H_{6b} appear as a typical pair of AB doublets, one of which is split further (J = 1.5 Hz). For compound **16** these protons have nearly identical chemical shifts and appear as a broad unresolved singlet, since $J_{6a\text{-}1}$ is very small. Previous NMR studies (2,3,5) of azabicyclo[2.2.1]heptane systems have shown that the coupling constant between a bridgehead proton and a vicinal *endo* proton is ~ 0. Consequently the AB doublet which is further split can be assigned to the *exo* proton H_{6a}. This small, yet clearly discernible, coupling between H_{6a} and H_1 was the basis for assigning H_1. When each of the two low field signals (H_1 and H_4) were subjected to double irradiation, only one succeeded in collapsing the H_{6a} signal into a sharp AB doublet.

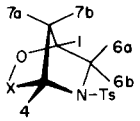
The remaining ring protons H_{7a} and H_{7b} characteristically appear as the highest field signals. For compounds **7** and **15** these protons have nearly identical chemical shifts and appear as a broadened singlet. The bridge protons in **11**, **14** and **16** have different chemical shifts. Each signal is essentially a doublet (J_{gem} = 11 cps) that is broadened by further smaller couplings. One signal is always broader and more complex than the other. This absorption is assigned to H_{7a} since it is expected that this proton should display long range coupling with H_{6b}. It is well documented (2,17,18) that considerable spin-spin coupling occurs between protons three carbons removed if they occupy a "planar W" configuration. In the bicyclo[2.2.1]heptane system, only the *endo* proton (H_{6b}) and H_{7a} fulfill this stereospecific requirement for long range coupling (19).

EXPERIMENTAL

Melting points were taken on a Thomas Hoover capillary m.p. apparatus and are uncorrected. IR spectra were recorded as potassium bromide pellets using a Perkin-Elmer 237B grating spectrometer. UV spectra were recorded on a Cary Model 14 spectrometer in ethanol solution. NMR spectra were obtained on a Varian A-60D spectrometer using deuteriochloroform as solvent with 1% TMS as an internal standard. Elemental analyses were

TABLE I

NMR Data for Substituted 2-Oxa-5-azabicyclo[2.2.1]heptanes



Compound	X	Chemical Shifts (δ)						Coupling Constants (Hz)		
		H_1	H_4	H_{6a}	H_{6b}	H_{7a}	H_{7b}	$J_{6a\text{-}6b}$	$J_{7a\text{-}7b}$	$J_{6a\text{-}1}$
7	$C{=}C(CO_2CH_3)_2$	5.15	5.85	3.63	3.40	1.97	1.97	10.5	---	1.4
11	$C(OCH_3)CH(CO_2CH_3)_2$	4.54	4.65	3.07	3.30	1.96	0.86	10	10.5	1.5
14	C=O	4.47	5.04	3.60	3.24	1.89	2.19	10.5	11	1.5
15(a)	$C{=}C(CO_2CH_3)(COCH_3)$	5.15	5.78	3.62	3.39	1.98	1.98	10.6	---	1.6
16(b)	$C(CH_3)_2$	4.36	4.02	3.17	3.17	1.93	0.98	---	11	---

(a) The major product isolated from the reaction of **3** with sodio methylacetoacetate, m.p. 108.5-109°; $[\alpha]_D^{21}$ + 20.6 (C 1%, ethanol); ir (potassium bromide); 1656 cm^{-1} (C=C), 1717 and 1700 cm^{-1} (C=O). *Anal.* Calcd. for $C_{17}H_{19}NO_6S$: C, 55.88; H, 5.24; N, 3.83. Found: C, 55.94; H, 5.18; N, 3.82. (b) A trace product (< 1%) from the reaction of **3** with dimethylcadmium, m.p. 129.5-130.5°; $[\alpha]_D^{21}$ + 6.4 (C 0.5%, ethanol); ir (potassium bromide); 1339 and 1157 cm^{-1} (*N*-Ts), 1095 cm^{-1} (C-O). *Anal.* Calcd. for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59.91; H, 6.74; N, 4.88.

performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York. The Rf values were determined on Eastman Chromagram sheets of silica gel with fluorescent indicator.

N,O-Ditosylhydroxy-L-proline Acid Chloride (**3**).

Method A (7).

N,O-Ditosylhydroxy-L-proline (3) was neutralized with 1*N* sodium hydroxide and the solution lypoholized. The sodium salt was immediately covered with dry benzene, cooled, and a 5-fold excess of oxalyl chloride cautiously added while stirring. After the ebullition of gas had ceased the mixture was warmed to 25° and stirred an additional 30 minutes. All excess oxalyl chloride and benzene was removed *in vacuo* and the residue of crude product was employed as such in subsequent reactions.

Method B.

A solution of *N,O*-ditosylhydroxy-L-proline in anhydrous THF was stirred overnight with one equivalent of lithium hydride. The solvent was removed *in vacuo* and the lithium salt covered with petroleum ether (30-60°). A 4-fold excess of oxalyl chloride was added and the mixture stirred 12 hours at 25°. The remaining oxalyl chloride and solvent were removed *in vacuo*, yielding crude acid chloride; ir (film) 1807 cm^{-1} (COCl).

The presence of acid chloride **3** in the crude residues was shown by its conversion to the known (3) methyl ester **10**. The crude residue was dissolved in methanol and the methanol then immediately removed *in vacuo*. The solid residue was identical in all respects (IR, NMR, m.p. and Rf value) (3) to authentic methyl ester **10**. In all cases the yield of methyl ester **10** was >90%.

Reaction of Dimethylmalonate Anion with **3**.

A solution of **3** (4.6 g., 0.01 mole) in 50 ml. of dry benzene was added to 0.0125 mole sodio dimethylmalonate in anhydrous ether. The mixture was stirred at room temperature for 16 hours, heated at 50° for 2.5 hours, then poured into 400 ml. of water and the aqueous phase extracted with ether. After drying over magnesium sulfate and removing solvent 4.0 g. of a glass was recovered. Acidification of the aqueous phase and extraction with ethyl acetate yielded 0.6 g. *N,O*-ditosylhydroxy-L-proline.

The crude ether extract was analyzed by TLC using ether as solvent first, followed by 5% methanol-chloroform and visualized with iodine. The extract contained dimethylmalonate, Rf 0.8, and two other components, Rf 0.5 and 0.6, which were separated and purified by fractional crystallization from aqueous ethanol. This yielded 1.3 g. (39%) of *N*-tosyl-2-oxa-3-dicarbomethoxymethylene-5-azabicyclo[2.2.1]heptane (**7**), m.p. 124-124.5°, TLC Rf 0.5, $[\alpha]_D^{21}$ + 156.1 (c 1%, ethanol); ir (potassium bromide) 1631 cm^{-1} (C=C), 1714 and 1737 cm^{-1} (esters); UV λ max 231 nm (ε, 20,000), 250 (ε, 15,000).

Anal. Calcd. for $C_{17}H_{19}NO_7S$: C, 53.53; H, 5.02; N, 3.67. Found: C, 53.62; H, 5.11; N, 3.62.

The other product (0.7 g., 16%) was 2,2-dicarbomethoxy-1-(*N,O*-ditosylhydroxy-L-prolinoxy)-1-(*N*-tosyl-*trans*-4-tosyloxy-2-pyrrolydinylethylene (**8**), m.p. 92-99°; TLC Rf 0.6; $[\alpha]_D^{21}$ -96.1 (c 1%, methanol); ir (potassium bromide) 1650 cm^{-1} (C=C), 1731 and 1787 cm^{-1} (C=O).

Anal. Calcd. for $C_{43}H_{46}N_2O_{16}S_4$: C, 52.97; H, 4.76; N, 2.87. Found: C, 52.92; H, 4.48; N, 2.81.

The reaction of **3** with the magnesio (20) or thallio (11) dimethylmalonate was carried out in the manner described above.

Dimethyl 2-(*N,O*-Ditosylhydroxy-L-prolinoyl)malonate (**4**).

A solution of **3** (4.6 g., 0.01 mole) in 100 ml. of anhydrous THF was added to 0.011 mole of sodio dimethylmalonate in THF. The mixture was stirred 45 seconds, acidified with ethereal hydrogen chloride, water added, and the aqueous phase extracted with ether. The extracts were dried with sodium sulfate and the ether removed *in vacuo* yielding 5.3 g. (96%) of **4** as an oil which was not further purified but used as such in subsequent reactions.

Reaction of Dimethylmalonate Anion with **4**.

A solution of **4** (5.3 g., 0.01 mole) in 100 ml. of anhydrous methanol was added to 0.02 mole of sodio dimethylmalonate in anhydrous methanol and the mixture stirred 4 hours at 25°. The mixture was acidified with ethereal hydrogen chloride and the solvent removed *in vacuo*. Water was added to the residue and the aqueous solution extracted with ether. After drying with sodium sulfate, the solution was concentrated *in vacuo* until a solid began to precipitate. The mixture then was refrigerated overnight and the solid *N*-tosyl-2-oxa-3-dimethylmalonyl-3-methoxy-5-azabicyclo-[2.2.1]heptane (11) collected. Recrystallization from absolute ethanol yielded 0.7 g. (17%) of **11**, m.p. 170-171°, TLC Rf 0.38 (using ether); $[\alpha]_D^{21}$ + 10.6 (c 1%, ethanol); ir (potassium bromide) 1763 and 1775 cm^{-1} (esters).

Anal. Calcd. for $C_{18}H_{23}NO_8S$: C, 52.29; H, 5.61; N, 3.39. Found: C, 52.15; H, 5.55; N, 3.39.

The mother liquor contained **7** TLC Rf 0.23.

The reaction of **4** with magnesio dimethylmalonate was conducted in the same manner except that the reaction mixture was refluxed for 24 hours.

N-Tosylallohydroxy-L-proline lactone (**14**).

N,O-Ditosylhydroxy-L-proline (3) was reacted according to the procedure of Witkop (21) described for *N*-acetyl-*O*-tosylhydroxy-L-proline. Crystalline **14** has m.p. 105°; $[\alpha]_D^{21}$ + 33.5 (c 1%, ethanol); ir (potassium bromide) 1789 cm^{-1} (lactone).

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 53.99; H, 4.83; N, 5.20.

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