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ELECTROPHILIC ATTACK ON BIASED ISOMERIC NITROALKYLATED ENAMINES

STEREOSPECIFIC HYDROLYSES OF THE RESULTING ADDUCTS

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Abstract—Stereoisomeric trisubstituted nitroalkylated enamines of 4-t-butylcyclohexanone react with diethyl azodicarboxylate affording enaminic adducts, which were hydrolysed under kinetically controlled conditions and examined.

1-Nitropropene (1NP) reacts with the morpholino enamine of 4-t-butylcyclohexanone leading to two stereoisomers **1** and **2**.[1] We have now chosen these substrates as anancomeric molecules for further studies on the reactivity of diethyl azodicarboxylate (DAD). The structures of the resulting enamines are examined as well as their hydrolyses to 2,6-disubstituted-4-t-butylcyclohexanones.

RESULTS

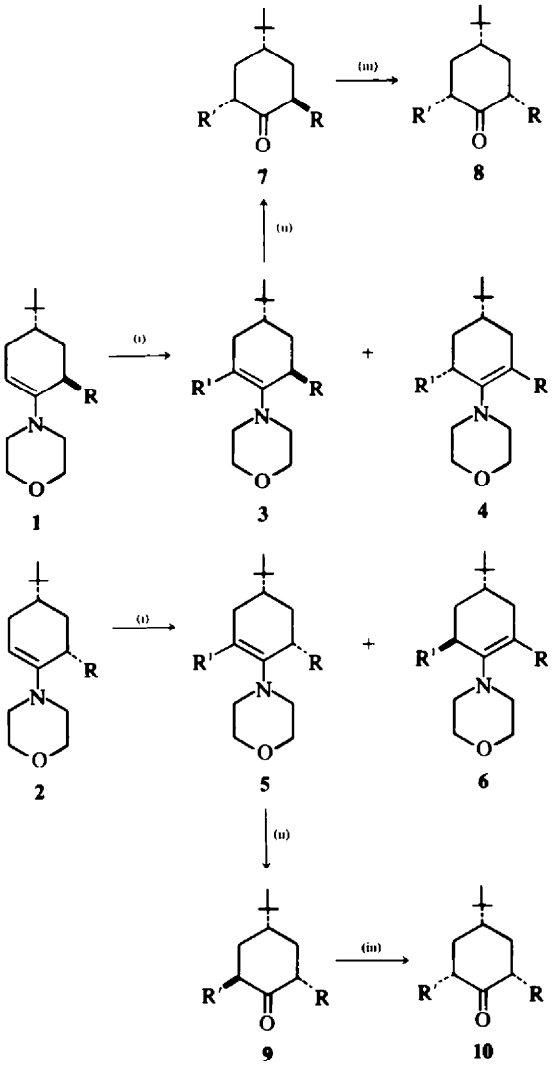
The *trans* stereoisomer **1** reacts with DAD at 5°, leading to a 90:10 mixture of **3** and **4** (Scheme 1). The PMR analysis of **3** does not show any absorption relative to the proton geminal to the hydrazodicarboxylate group, whereas **4** exhibits this absorption at 4.98 δ with $W_H = 27$ Hz, which accounts for the axial conformation of the proton itself.[2] On the other hand the β-nitroisopropyl group in **3** maintains its configuration and conformation, as shown by the PMR shift and pattern of the nitromethylenic protons, if compared with those of **1**.

The *cis* stereoisomer **2** reacts similarly and affords a mixture of **5** and **6** in the ratio 70:30 (Scheme 1). Compound **5** exhibits no PMR signal for the proton geminal to R', whereas in **6** it appears at 4.95 δ with $W_H = 16$ Hz, which demonstrates the equatorial conformation of the proton in question.[2] As to the R group, enamine **5** shows the same chemical shift and pattern for the nitromethylenic proton signal as **2**, thus indicating that its configuration and conformation is still the same.

Surprisingly enamines **3**, **4**, **5** and **6** show different behaviour towards hydrolysis. When they are subjected to acid-catalysed hydrolysis, under kinetically controlled conditions, **3** undergoes rapid hydrolysis in 6 hr, **5** in 24 hr at least, and **4** and **6** fail to react.

Hydrolysis of **3** leads to the less stable ketone **7** in which the R' group is equatorial and the nitroalkyl group axial, as shown by the PMR analysis. Compound **7** can be completely converted to the all-*cis* isomer **8**, by acidic catalyst under reflux in benzene. Similarly **5** affords the ketone **9**, in which the hydrazino dicarbethoxy group is axial while the nitroalkyl group equatorial, as indicated by the PMR analysis. By equilibration, **9** is converted to its isomer **10**, in which the R' group is now equatorial (Scheme 1).†

Although **8** and **10** are all-*cis*, they are diastereoisomers, since the β-nitroisopropyl group contains an asymmetric



Scheme 1. R = $-CH(CH_3)-CH_2NO_2$; R' = $-N(CO_2Et)-NHCO_2Et$. (i) DAD, 5°C; (ii) H^+, H_2O; (iii) TsOH, 80°C.

†The relative configurations of the ketones **7**, **8**, **9** and **10** have been assigned on the basis of the chemical shifts and patterns of the nitromethylenic proton signals, as already done in our previous work.[1]

C atom. The configuration of **8** is in fact *erythro*, relative to the C_2–C_α bond, whereas that of **10** is *threo*.

DISCUSSION

1. *Reactivity of DAD on the substrates.* The conditions under which the reactions are carried out are strictly kinetically controlled. Not only the ketones but also the enamines in fact can be equilibrated.[3] By equilibration they afford mixtures of isomeric enamines in which the compound **6** is formed in considerable predominance (nearly 75%) over all the other diastereoisomers. The stereochemical course we postulate is based on the relative stability of the intermediates, as we think that the transition states are intermediate-like rather than reactant-like.

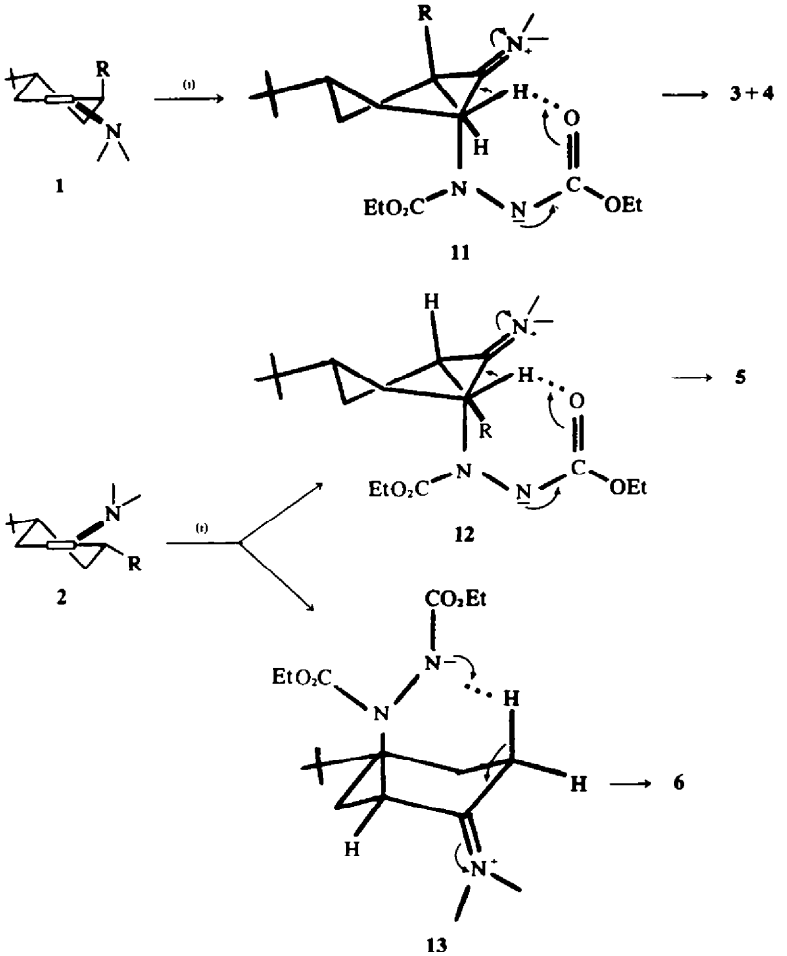
The attack of DAD on the *trans* isomer **1** seems to occur from the α-direction rather than from the β-direction,[4] in spite of the fact that the resulting intermediate **11** is in twist conformation (Scheme 2). The intermediate derived from the antiparallel attack in fact would suffer from a 1,3-diaxial interaction between the entered bulky substituent and the axial R group. On the other hand the formation of **11** seems necessary in view of the obtainment of **4**, by abstraction of the proton geminal to R, through a boat-like cyclohexane ring.

Compound **2** undergoes the attack of DAD from both α and β directions, leading to two intermediates **12** and **13** and then to **5** and **6** respectively (Scheme 2). Intermediate **13** would seem more favourable, being in the chair conformation, but the presence of an $A_{1,3}$ strain[5] probably enhances its energy, so that the formation of **12**, in which this interaction is somewhat released, becomes important. The ratio **5**:**6** in fact is 70:30. The stereoelectronically less favourable abstraction of the equatorial protons in **11** and **12** is a consequence of the prevailing steric factors over the electronic ones. In their chair-shaped conformational isomers in fact, strong $A_{1,3}$ strains would be present, which we think to be energetically less favourable than the abstraction of *quasi*-equatorial protons in the twist forms. In any case, abstraction of the protons occurs in a fast step, subsequent to the attack of the electrophile, which is generally considered the slow, rate-determining step.

2. *Hydrolysis of enaminic adducts.* Acid-catalyzed hydrolysis of **3** under kinetically controlled conditions affords the ketone **7** in quantitative yield. The structural assignments, based on PMR analysis, lead us to the conclusion that the protonation must be necessarily stereospecifically axial. The pathways to **7** are indicated in Scheme 3. Ketone **7** can be easily converted to its isomer **8**, and this is another proof of the mechanism suggested.

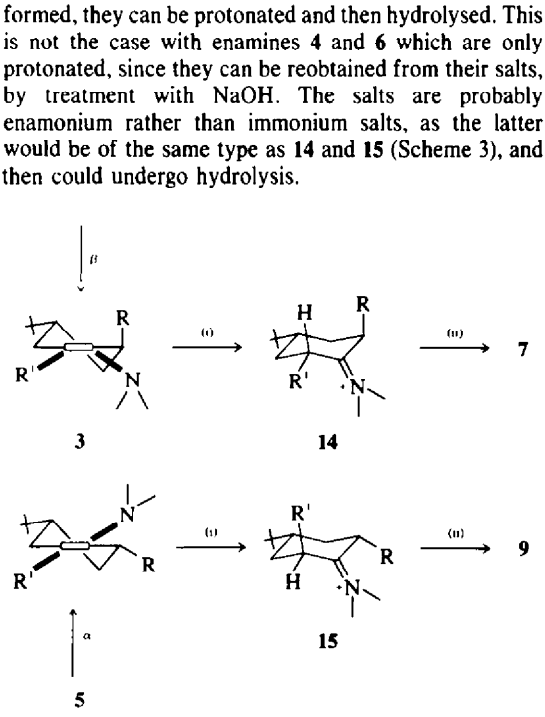
Enamine **5** reacts similarly and affords the ketone **9**. The structural assignments based on PMR analysis and on the fact that **9** equilibrates into **10**, permit us to say that the protonation of **5** is stereospecifically equatorial (Scheme 3).

Hydrolyses have confirmed the stereospecificity of protonation, as we have usually found also for non-biased



Scheme 2. R = –CH(CH₃)–CH₂NO₂. (i) DAD, 5°C.

systems.[2] This is in contrast with the recent results of Johnson *et al.*[6] However we agree with their suggestions that the behaviour of our substrates is unusual. It surely depends upon the presence of the hydrazodicarboxylate group, which is very polar and hence very solvated by the protic medium in which the hydrolyses are carried out. On the other hand we do not think that it can work as a proton-acceptor and donor towards the ring itself, through an intermediate of the same type as that generating the enamine. This would mean that just as the enamines are formed, they can be protonated and then hydrolysed. This is not the case with enamines **4** and **6** which are only protonated, since they can be reobtained from their salts, by treatment with NaOH. The salts are probably enamonium rather than immonium salts, as the latter would be of the same type as **14** and **15** (Scheme 3), and then could undergo hydrolysis.



Scheme 3. R = $-CH(CH_3)-CH_2NO_2$; R' = $-N(CO_2Et)-NHCO_2Et$. (i) H^+; (ii) H_2O.

EXPERIMENTAL

IR spectra were obtained using a Perkin–Elmer 257 spectrometer and PMR spectra were recorded on a Jeol JNM-C-60HL instrument. PLC were prepared using extra pure SiO_2 Merck (70-325 mesh ATMS).

Reaction of trans - threo - 1 - *morpholino* - 2(*β* - *nitroisopropyl*) - 4 - *t* - *butyl* - *cyclohexene* (**1**) *with diethyl azodicarboxylate.* Diethyl azodicarboxylate (1.6 g, 9 mmoles) in dry ether was added dropwise to a soln of **1** (2.8 g, 9 mmoles), at 5°. The mixture was kept at 5° for 48 hr. Removal of the solvent left a yellow oil which was treated with benzene–ligroin. A solid product **3** (3.5 g, 80%) was isolated, m.p. 136–38° (Found: C, 56.6; H, 8.28; N, 11.34. $C_{23}H_{40}N_4O_7$ requires: C, 57.0; H, 8.32; N, 11.56%). IR (Nujol): 3280, 3190 cm^{-1} (NH); 1760, 1730, 1700 cm^{-1} (CO_2Et); 1645 cm^{-1} (C=C–N); 1545, 1375 cm^{-1} (NO_2). PMR ($CDCl_3$): 0.90 δ (*t*-Bu, s); 1.26 δ (CH_2CH_3, t); 2.25 δ (CH_2NCH_2, m): 2.90 δ (CH_2OCH_2, m): 4.23 δ (CH_2NO_2, CH_2CH_3, m): 7.20 δ (NH, s). The mother liquors were concentrated and chromatographed (eluent: acetone–benzene 4%). **3** (0.4 g, 10%) was separated along with **4** (0.4 g, 10%), m.p. 118–20°, from ether (Found: C, 56.6; H, 8.03; N, 11.0%). IR (Nujol): 3390 cm^{-1} (NH); 1755, 1710 cm^{-1} (CO_2Et); 1550, 1380 cm^{-1} (NO_2). PMR ($CDCl_3$): 0.90 δ (t-Bu, s); 1.25 δ (CH_2CH_3, t); 2.70 δ (CH_2NCH_2, m); 3.65 δ (CH_2OCH_2, m); 4.25 δ (CH_2NO_2, CH_2CH_3, m); 4.98 δ (CHNH, m(W_H = 27 Hz)); 6.12 δ (NH, s).

The enamine **3** (1.7 g, 3.5 mmoles) was hydrolysed with HCl 1N (0.12 g, 3.5 mmoles) in acetonitrile–water for 6 hr, neutralized with NaOH, and extracted with ether. Removal of the solvent left the ketone **7** (1.3 g, 95%), m.p. 114–15°, from benzene–n-exane (Found: C, 55.80 H, 8.42; N, 10.30. $C_{19}H_{33}N_3O_7$ requires: C, 54.93; H, 8.01; N, 10.11%). IR (Nujol): 3380 cm^{-1} (NH): 1760, 1740, 1715 cm^{-1} (CO_2Et, CO); 1540, 1375 cm^{-1} (NO_2). PMR ($CDCl_3$): 0.95 δ (t-Bu, s); 1.24 δ (CH_2CH_3, t); 4.20 δ (CH_2CH_3, CH_2NO_2, m); 4.95 δ (CHNH, m (W_H = 24 Hz)).

The product **7** (0.5 g, 3.6 mmoles) was equilibrated with TsOH in refluxing benzene for 24 hr. **8** was obtained in quantitative yield, m.p. 90–1°, from benzene–n-exane (Found: C, 54.80 H, 8.33; N, 10.55. $C_{19}H_{33}N_3O_7$ requires: C, 54.93; H, 8.01; N, 10.11%). IR (Nujol): 3250 cm^{-1} (NH): 1765, 1755, 1710, 1690 cm^{-1} (CO_2Et, CO); 1555, 1375 cm^{-1} (NO_2). PMR ($CDCl_3$): 1.0 δ (t-Bu, s); 1.24 δ (CH_2CH_3, t); 4.13 δ (CH_2CH_3, q); 4.40 δ (CH_2NO_2, m); 4.60 δ (CHNH, m (W_H = 24 Hz)); 6.65 δ (NH, s).

Reaction of cis - threo - 1 - *morpholino* - 2 - (*β* - *nitroisopropyl*) - 4 - *t* - *butyl* - *cyclohexene* (**2**) *with diethyl azodicarboxylate.* Diethyl azodicarboxylate (1.3 g, 7 mmoles) in dry ether was added dropwise to a soln of **2** (2.3 g, 7 mmoles). The mixture was kept at 5° for 48 hr and afforded **5** (2.5 g, 70%), m.p. 182–83° (Found: C, 56.75; H, 8.34; N, 11.68. $C_{23}H_{40}N_4O_7$ requires: C, 57.01; H, 8.32; N, 11.56%). IR (Nujol): 3260, 3170 cm^{-1} (NH); 1720 cm^{-1} (CO_2Et); 1640 cm^{-1} (N–C=C); 1545, 1375 cm^{-1} (NO_2). PMR ($CDCl_3$): 0.89 δ (t-Bu, s); 1.25 δ (CH_2CH_3, t); 2.85 δ (CH_2NCH_2, m); 3.64 δ (CH_2OCH_2, m); 4.18 δ (CH_2CH_3, q); 4.35 δ (CH_2NO_2, d (J = 7.5 Hz)); 6.90 δ (NH, s). Light petroleum was added to the mother liquors and **6** crystallized (1.0 g, 30%), m.p. 134–35° (Found: C, 57.10; H, 8.65; N, 11.30. $C_{23}H_{40}N_4O_7$ requires: C, 57.01; H, 8.32; N, 11.56%). IR (Nujol): 3300, 3160 cm^{-1} (NH); 1750, 1700 cm^{-1} (CO_2Et); 1650 cm^{-1} (N–C=C); 1545, 1375 cm^{-1} (NO_2). PMR ($CDCl_3$): 0.84 δ (t-Bu, s); 1.25 δ (CH_2CH_3, t); 2.64 δ (CH_2NCH_2, m); 3.64 δ (CH_2OCH_2, m); 4.30 δ (CH_2NO_2, CH_2CH_3, m); 4.95 δ (CHNH, m (W_H = 16 Hz)); 6.0 δ (NH, s).

The enamine **5** (2.0 g, 4 mmoles) was hydrolysed with HCl 1N (0.14 g, 4 mmoles) for 24 h, in acetone–water. After removal of the solvent, **9** was isolated (1.8 g, 90%), m.p. 120–22°, from benzene–ligroin (Found: C, 54.70; H, 7.97; N, 10.10. $C_{19}H_{33}N_3O_7$ requires: C, 54.93; H, 8.01; N, 10.11%). IR (Nujol): 3300 cm^{-1} (NH): 1740, 1710, 1700 cm^{-1} (CO_2Et, CO); 1550, 1375 cm^{-1} (NO_2). PMR ($CDCl_3$): 0.95 δ (t-Bu, s); 1.25 δ (CH_2CH_3, t); 4.18 δ (CH_2CH_3, q); 4.46 δ (CH_2NO_2, d (J = 6.75 Hz)); 4.59 δ (CHNH, m (W_H = 16 Hz)); 6.85 δ (NH, s).

The ketone **9** (1.0 g, 7.2 mmoles) was equilibrated with TsOH under reflux in benzene for 24 h and afforded **10** in quantitative yield, m.p. 133–35°, from ethanol (Found: C, 54.81; H, 8.14; N, 9.97. $C_{19}H_{33}N_3O_7$ requires: C, 54.9; H, 8.01; N, 10.11%). IR (Nujol): 3310 cm^{-1} (NH): 1750, 1715, 1695 cm^{-1} (CO_2Et, CO); 1540, 1375 cm^{-1} (NO_2). PMR ($CDCl_3$): 0.98 δ (t-Bu, s); 1.24 δ (CH_2CH_3, t); 4.18 δ (CH_2CH_3, q); 4.42 δ (CH_2NO_2, d (J = 6.75 Hz)); 4.80 δ (CHNH, m (W_H = 27 Hz)); 6.87 δ (NH, s).

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