Enamine Chemistry. Part 27.[1] The Effect of Additional α- and β-Heteroatoms on the p_π-Conjugation and Reactivity of Enamines. Sub- or Super-Enamines?

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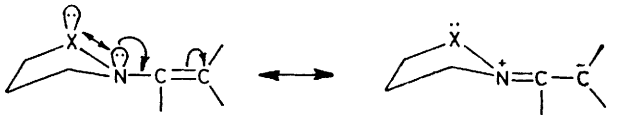
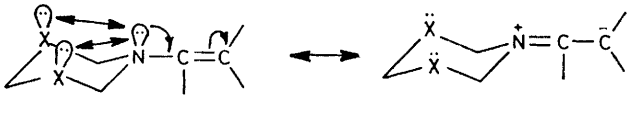
Enamines derived from isoxazolidine and 1,3-dioxa-5-azacyclohexane have been prepared. The effect of the addition a α- or β-heteroatoms is to decrease the p_π-conjugation between the nitrogen lone pair of electrons and the π-electrons of the double bond, as reflected in the spectral properties of the enamines and their reactivity with electrophiles. The reasons for this are discussed.

THE increased p_π-conjugation in enamines derived from pyrrolidine compared to all other secondary amines so far utilised for this purpose is well known from their increased chemical reactivity [2] and their reduced stereoselectivity of reaction,[3] as well as from spectroscopic [4] and, more recently, *X*-ray crystallographic evidence.[5] In an attempt to increase this degree of p_π-overlap still further we have investigated the effect of incorporating additional heteroatoms into the amine moiety of enamines derived from five- and six-membered cyclic amines. The idea was that the lone pair–lone pair electron repulsion illustrated in partial structures (1a) and (2a) could be alleviated by the escape route provided by greater involvement of the nitrogen lone pair with the π-electrons of the double bond as in (1b) and (2b). Clearly whether an increase in the electron density will occur at the C-β position of the enamine will depend upon the relative magnitudes of this electron repulsion and that of the inductive electron attraction of the additional heteroatoms, which will operate in the opposite direction, and also upon whether the molecule can preferentially



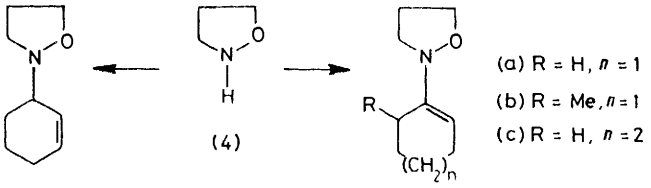
(1a) (1b)



(2a) (2b)

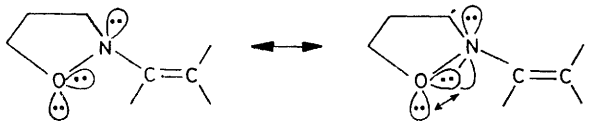
adopt a conformation which removes or minimises the lone pair repulsions by other means.

As an example of an amine containing an additional α-heteroatom we selected isoxazolidine (4).[6] Enamines from this amine have not been reported before and we found that the normal methods for enamine formation [2,7] failed owing to the low reactivity and low thermal stability of isoxazolidine which precluded the use of higher temperatures. Condensation with 3-bromocyclohexene readily occurred to give 3-isoxazolidin-2-ylcyclohexene (3) but attempted base-catalysed double-bond rearrangement [8] of the allylamine to the enamine also failed. Eventually several enamines (5) from isoxazolidine were prepared by the titanium tetrachloride route,[9] normally reserved for highly hindered ketones, but the low thermal stability of the heterocyclic ring prevented the enamines from being obtained in an analytically pure state. However, their structures were clearly confirmed by the spectral data (see Table) which showed the correct molecular ions, the absence of carbonyl absorption and the presence of carbon–carbon double bond absorption at 1 650—1 660 cm^{-1}, and olefinic signals at δ 5.05—5.3 in the ^1H n.m.r. spectra. The low-field shift of the olefinic signal in (5a) compared to that of the corresponding pyrrolidine and morpholine enamines (δ 4.17 and 4.55 respectively [4a]) indicated ominously low p_π-conjugation; this was confirmed by the low reactivity of these enamines with the normally highly reactive electrophilic olefins, acrylonitrile [10] and diethyl azodicarboxylate.[11] Reaction of the enamine (5a) with acrylonitrile did occur, at room temperature, but much more slowly than the corresponding pyrrolidine enamine,



(3) (4) (5)

(a) R = H, *n* = 1
(b) R = Me, *n* = 1
(c) R = H, *n* = 2

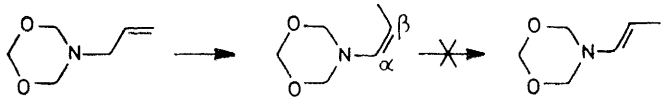


(6a) (6b)

the reaction of which was shown by Fleming and Harley-Mason to be complete in 20 min.[10] In the case of (5b) no reaction apparently occurred at room temperature, again in contrast to the increased reactivity of the corresponding pyrrolidine enamine.[10] With both enamines reaction with diethyl azodicarboxylate resulted only in hydrogen abstraction to give diethyl hydrazodicarboxylate.

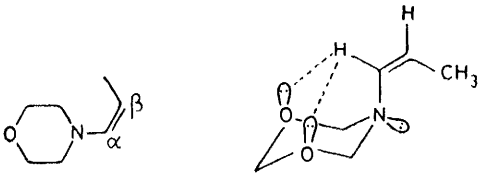
So it appears that the amine moiety in the enamines (5a—c) is adopting a conformation which will minimise electron repulsion, by moving the lone pairs out of alignment, rather than by transfer of electron density into the double bond. Indeed, it is possible for the amine to take up a conformation in which electron repulsion between one of the oxygen lone pairs and a developing p-orbital on the nitrogen would oppose the rehybridisation of the nitrogen necessary for such electron transfer to take place [see partial structures (6a) and (6b)]. However in any case the conjugation of the nitrogen lone pair with the double bond is clearly inhibited by the inductive electron withdrawal of the adjacent oxygen atom.

The incorporation of additional heteroatoms β to the enamine nitrogen was next achieved by the synthesis of an enamine from 1,3-dioxa-5-azacyclohexane. The parent amine is not known so the enamine was prepared indirectly by reaction of allylamine with formaldehyde to give 5-allyl-1,3-dioxa-5-azacyclohexane (7). This re-



(7) (8) (9)

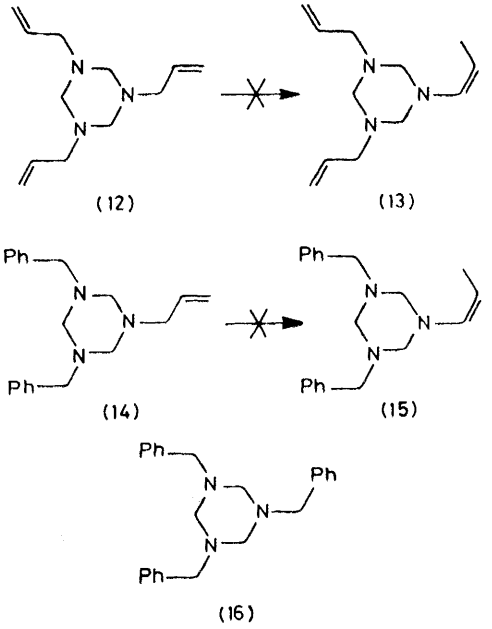
arranged to the enamine of propionaldehyde, 5-prop-1-enyl-1,3-dioxa-5-azacyclohexane (8), on treatment with base, but more slowly than the corresponding *N*-allyl derivatives of pyrrolidine and morpholine.[4c] This product gave single peaks at δ 4.7 and 5.1 in the n.m.r. spectrum characteristic of 1,3-dioxa-5-azacyclohexanes.[12] The coupling constant for the olefinic protons (J = 8 Hz) indicated that the *cis*-enamine had been formed,[8] as would be expected under the conditions used. First indications that the desired increase in p_π-conjugation had not been achieved came from the chemical shifts of the olefinic protons of the enamine double bond which appeared at low field. The β-proton gave a signal at δ 5.1, indicating reduced p_π-conjugation compared with the *cis*-isomer of the morpholine enamine of propionaldehyde (10) ($\delta_{H\text{-}\beta}$ 4.6), and the α-proton appeared at δ 6.25 suggesting greater inductive electron withdrawal compared to the morpholine ring since the α-proton of *cis*-morpholinoprop-1-ene (10) gave a signal at δ 5.5. This was confirmed by the ^{13}C n.m.r. spectrum which showed the C-β signal of (8) at δ 111.0, at lower field compared to the C-β signal of the morpholine enamine (10) (δ 107.5).[4c] In the *trans*-isomer (9) the C-β signal would be expected to be at considerably higher field (*i.e.* δ 95.8 for *trans*-morpholinoprop-1-ene [4c]). The chemical properties of the enamine which we have investigated are also indicative of reduced reactivity arising from reduced p_π-conjugation. Thus all attempts to rearrange *cis*-(8) to *trans*-(9), by treatment with protic solvents [8] or heating with toluene-*p*-sulphonic acid in various solvents failed, and attempts to hydrolyse the enamine



(10) (11)

with aqueous acid resulted in preferential fission of the heterocyclic ring.

The reduced p_π-conjugation in enamine (8) can be attributed to three factors. First there is the inductive electron withdrawal of the two oxygen atoms. Second, as Katritzky *et al.* have clearly demonstrated,[12] an alkyl group in 5-alkyl-1,3-dioxa-5-azacyclohexanes will preferentially adopt an axial orientation. This has been attributed to removal of 1,3-syn-diaxial interactions, relief of adverse anomeric effects,[12] distortion of the nitrogen valency angles, and weak attractive interactions between the alkyl group and the β-heteroatoms.[13] It would therefore appear that, in the case of 5-prop-1-enyl-1,3-dioxa-5-azacyclohexane, conformational stabilization has not been achieved by increased p_π-conjugation in the equatorial conformer, as we had hoped, but by ring or nitrogen inversion giving the axial



(12) (13) (14) (15) (16)

conformer (11). Thirdly, the striking lack of p_π-conjugation which even prevents *cis–trans* isomerism [(8) ⟶ (9)] may be due to interactions between the oxygen lone pairs with the propenyl residue which cause the latter to adopt a conformation in which the nitrogen

lone pair is orthogonal to the π-orbital of the double bond [as in (11)].

Since it is known [13,14] that 1,3,5-trialkyl-1,3,5-triazacyclohexanes exist in preferred conformations with one or two alkyl groups equatorially orientated, in order to reduce 1,3-*syn*-diaxial interactions, attempts have been made to synthesize triazacyclohexane enamines. Accordingly 1,3,5-triallyl-1,3,5-triazacyclohexane (12) was prepared from formaldehyde and allylamine, and 1-allyl-3,5-dibenzyl-1,3,5-triazacyclohexane (14) was obtained from the reaction of 5-allyl-1,3-dioxa-5-azacyclohexane with two equivalents of benzylamine. However all attempts to induce base-catalysed rearrangement to the enamines (13) and (15) were unsuccessful.

In conclusion it is clear that the expected increase in p_π-conjugation has not been realised simply because the compounds so far examined have been able to adopt conformations in which the lone pair repulsions have been eliminated. However, we remain convinced that if the right combination of structural features could be realised, so that the enamine double bond was forced into an equatorial orientation and the nitrogen lone pair was held in a 1,3-*syn*-orientation with respect to another lone pair, then greater p_π-conjugation and increased reactivity could be achieved.

Spectral data

Compound	Mass spectrum (*m/e*) Found		Reqd.	$\nu_{max.}$/cm^{-1} (film)	^{1}H N.m.r. ($CDCl_3$) (δ)
(5a)	153.1151	$C_9H_{15}NO$	153.1153	1 660	5.15 (s, 1 H, =CH), 3.87 (t, 2 H, OCH_2), 3.15 (t, 2 H, NCH_2), 2.55—1.2 (m, 10 H, CH_2).
(5b)	167.1308	$C_{10}H_{17}NO$	167.1309	1 650	5.05 (t, 1 H, =CH), 3.83 (t, 2 H, OCH_2), 3.10 (t, 2 H, NCH_2), 2.65—1.35 (m, 9 H, CH_2 and CH), 1.15 (d, 3 H, CH_3).
(5c)	167.1308	$C_{10}H_{17}NO$	167.1309	1 650	5.30 (t, 1 H, =CH), 3.92 (t, 2 H, OCH_2), 3.10 (t, 2 H, NCH_2), and 2.75—090 (m, 12 H, CH_2).

EXPERIMENTAL

Isoxazolidine [6] and 5-allyl-1,3-dioxa-5-azacyclohexane [15] were prepared by the literature methods.

3-Isoxazolidin-2-ylcyclohexene (3).—3-Bromocyclohexene [16] (8.05 g, 0.05 mol) and a solution of sodium hydroxide (2.5 g, 0.625 mol) in water (5 ml) were added dropwise simultaneously from two dropping funnels to a solution of isoxazolidine (3.65 g, 0.05 mol) in water (9 ml) at room temperature; the reaction mixture was then heated for 4 h at 60 °C. Two layers formed and the upper layer was separated, dried (KOH pellets) and distilled to give 3-isoxazolidin-2-ylcyclohexene (1.8 g, 50%), b.p. 118—120 °C/20 mmHg (Found: M^+, 153.115 3.$C_9H_{15}NO$ requires M, 153.1153), $\nu_{max.}$ (film) 1 650 cm^{-1} (C=C); δ_H ($CDCl_3$) 5.83 (s, 2 H, =CH), 3.9 (t, 2 H, OCH_2), 3.0 (m, 3 H, $CHNCH_2$), 2.5—1.5 (m, 8 H, CH_2); δ_C (neat liquid) 127.9, 127.5 (d, =CH), 65.0 (t, OCH_2), 61.1 (d, CHN), 51.6 (t, CH_2N), 28.9, 27.4, 25.6, and 20.1 (t, CH_2). Attempted double-bond rearrangement of this product to give 1-isoxazolidin-2-ylcyclohexene (5a), by heating with potassium t-butoxide in dry dimethyl sulphoxide, was unsuccessful. Distillation of the crude mixture apparently resulted in ring opening and polymerisation.

Condensation of Cyclic Ketones with Isoxazolidine: General Method of Enamine Formation.—A solution of the ketone (0.01 mol) and triethylamine (5 ml) in dry benzene (4 ml) was added to the isoxazolidine (3.65 g, 0.05 mol) and the mixture stirred for 30 min below 10 °C. A solution of titanium tetrachloride (1.90 g, 0.01 mol) in dry benzene (10 ml) was then added dropwise during 1 h with cooling below 10 °C. The mixture was then allowed to warm to room temperature (23 °C) while being stirred overnight (*ca.* 20 h). The reaction mixture was then filtered and the volatiles removed from the filtrate *in vacuo* below 50 °C. The residual liquid was extracted with ether under a stream of dry nitrogen and the ether extracts evaporated to give the crude enamine which could not be purified owing to decomposition on attempted distillation. The relevant spectroscopic data is given in the Table.

Reactions of 1-Isoxazolidin-2-ylcyclohexene (5a).—(*a*) *With acrylonitrile.* A mixture of acrylonitrile (0.66 g) and 1-isoxazolidin-2-ylcyclohexene (1.0 g) was stirred at room temperature for 48 h. The resulting viscous mass was extracted with ether and the ether extract separated and evaporated to dryness. The residual mass was stirred with water (5 ml) at room temperature for 24 h. The mixture was extracted with ether, dried ($MgSO_4$), and evaporated to give crude 2-β-cyanoethylcyclohexanone (0.5 g, 50%) which was purified by preparative t.l.c. on silica (5% acetone in chloroform; R_F 0.5) (Found: M^+, 151.099 7. $C_9H_{13}NO$ requires M, 151.099 7); $\nu_{max.}$ (film) 2 245 (C≡N) and 1 705 cm^{-1} (CO); δ_H ($CDCl_3$) 3.0—1.0, complex.

(*b*) *With diethyl azodicarboxylate.* A solution of 1-isoxazolidin-2-ylcyclohexene (0.765 g, 0.005 mol) in dry ether (4 ml) was added to diethyl azodicarboxylate (1.74 g, 0.01 mol) in dry ether (4 ml) at room temperature. The mixture was stirred for 2 h at room temperature and then kept for 7 days in the dark. The ether was then removed *in vacuo* to give a gummy mass which was dissolved in methanol (10 ml) and 10% hydrochloric acid (10 ml) added to the solution which was then kept in a refrigerator for 24 h. Water (20 ml) was added and the mixture extracted with ether, and the ether extract dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give diethyl hydrazodicarboxylate (0.2 g), m.p. 130—131 °C (from benzene) (Found: M^+, 176.079 7. $C_6H_{12}N_2O_4$ requires M, 176.079 7); δ_H ($CDCl_3$) 6.7 (s, 2 H, NH), 4.2 (q, 4 H, CH_2O), and 1.33 (t, 6 H, CH_3).

Reactions of 6-Methyl-1-isoxazolidin-2-ylcyclohexene (5b).—(a) *With acrylonitrile.* This reaction was carried out in the same way as that described above for (5a). After 65 h at room temperature the intensity of the enamine carbon–carbon double bond absorption showed no significant decrease in intensity. The experiment was therefore abandoned.

(b) *With diethyl azodicarboxylate.* The same reaction conditions as described for (5a) were used and again only diethyl hydrazodicarboxylate was isolated.

5-Prop-1-enyl-1,3-dioxa-5-azacyclohexane (8).—A mixture of 5-allyl-1,3-dioxa-5-azacyclohexane (7) (3.14 g, 0.024 mol)

and dry potassium t-butoxide (0.48 g) in dry dimethyl sulphoxide (5 ml) was stirred at 80 °C for 10 days under an atmosphere of dry nitrogen. The resulting mixture was then distilled under reduced pressure and the fraction boiling at 40 °C/1 mmHg was collected and cooled in a solid CO_2–acetone bath in order to freeze out the co-distilled dimethyl sulphoxide. The residual liquid was pipetted out to give crude 5-prop-1-enyl-1,3-dioxa-5-azacyclohexane (1 g, 32%) contaminated with dimethyl sulphoxide (Found: M^+, 129.079 4. $C_6H_{11}NO_2$ requires M, 129.078 9), $\nu_{max.}$ (film) 1 665 cm^{-1} (C=C); δ_H ($CDCl_3$) 6.25 (dm, 1 H, J = 8 Hz, =CH·N), 5.1 (s, 2 H, OCH_2O overlaid by a multiplet, 1 H, =$CHCH_3$), 4.7 (s, 4 H, OCH_2N), and 1.58 (dd, 3 H, J = 1.5 and 7 Hz, CH_3); δ_C 136.2 (=CH–N), 111.0 (=CH·CH_3), 94.35 (OCH_2O), 82.7 (OCH_2N), and 11.5 (CH_3). Attempts to cause this product to rearrange to the *trans*-isomer (9), by treatment with protic solvents [8] or toluene-*p*-sulphonic acid in various solvents, were unsuccessful. Only unchanged starting material was recovered or ring fission was observed. Similar results were obtained on attempted hydrolysis with hot or cold aqueous hydrochloric acid.

1,3,5-*Triallyl*-1,3,5-*triazacyclohexane* (12).—An aqueous solution of formaldehyde (37%) (8.0 ml, 0.1 mol) was added dropwise to allylamine (5.7 g, 0.1 mol) with stirring at 5—10 °C with cooling. The mixture was stirred for 1 h whilst it warmed to room temperature; it was then extracted with ether, and the ether extracts were dried and evaporated to give an oil distillation of which gave 1,3,5-triallyl-1,3,5-triazacyclohexane (4.5 g), b.p. 60—62 °C/0.1 mmHg (Found: M, 207.173 4. $C_{12}H_{21}N_3$ requires M, 207.173 5), δ_H ($CDCl_3$) 4.2, 4.8 (m, 9 H, CH=CH_2), 3.4 (s, 6 H, CH_2), and 3.1 (d, 6 H, CH_2CH=); δ_C 126.2 (CH=), 116.3 (CH_2=), 73.8 (NCH_2N), and 55.9 (CH_2CH=).

1-*Allyl*-3,5-*dibenzyl*-1,3,5-*triazacyclohexane* (14).—5-Allyl-1,3-dioxa-5-azacyclohexane (7) (5.6 g, 0.042 mol) was added to a mixture of benzylamine (9.8 g, 0.09 mol) and water (5.6 ml) at 0—5 °C with stirring. The mixture was stirred at room temperature overnight and then extracted with ether; the ether extracts were dried, evaporated, and the residual oil fractionated at reduced pressure (0.1 mmHg) to give 1-allyl-3,5-dibenzyl-1,3,5-triazacyclohexane (14) (3 g), b.p. 140—145 °C (Found: M^+, 307.204 8. $C_{20}H_{25}N_3$ requires M, 307.204 8), $\nu_{max.}$ (film) 1 645 cm^{-1} (C=C); δ_H ($CDCl_3$) 7.45 (s, 10 H, C_6H_5), 5.8, 5.2 (m, 3 H, CH=CH_2), 3.75 (s, 4 H, CH_2Ph), 3.45 (s, 6 H, CH_2), and 3.1 (d, 2 H, CH_2CH=); δ_C 138.2, 128.3, 127.75 (C_6H_5), 134.9 (CH=), 116.85 (CH_2=), 73.4 (NCH_2N), and 56.6 (CH_2Ph); and 1,3,5-tribenzyl-1,3,5-triazacyclohexane (16) (2 g), b.p. 150—160 °C (Found: M^+, 357. $C_{24}H_{27}N_3$ requires M, 357), δ_H ($CDCl_3$) 7.3 (s, 15 H, C_6H_5), 3.65, and 3.4 (s, 12 H, CH_2).

Attempted Double-bond Rearrangements.—(a) A mixture of 1,3,5-triallyl-1,3,5-triazacyclohexane (12) (2.07 g, 0.01 mol) and dry potassium t-butoxide (0.60 g, 0.053 mol) in dry dimethyl sulphoxide (5.0 ml) was heated at 80 °C for 21 days under dry nitrogen. The ^1H n.m.r. spectrum of the reaction mixture was recorded at various intervals of time but showed no significant differences from that of the starting material.

(b) 1-Allyl-3,5-dibenzyl-1,3,5-triazacyclohexane (14) (1.70 g) was treated with potassium t-butoxide (0.23 g) in the same manner, but again the ^1H n.m.r. spectrum of the reaction mixture showed no significant changes. Distillation of the reaction mixture gave only unchanged (14), b.p. 140—142 °C/0.15 mmHg.

The ^{13}C n.m.r. spectra were recorded at 20 MHz with a Varian CFT-20 spectrometer for neat liquids unless stated otherwise, the ^1H n.m.r. spectra were recorded at 60 MHz with a Varian EM 360 spectrometer, and the mass measurements were carried out with A.E.I. MS 9 or MS 12 mass spectrometers operating at 70 eV.

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