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CYCLOHEXANESPIROCOMPOUNDS FROM 1-AMINOCYCLOHEXENES AND PHENYLCARBAMOYLDIIMIDE.

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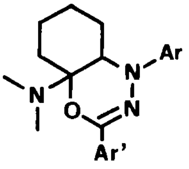
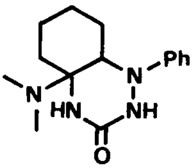
Abstract : The unexpected behaviour of phenylcarbamoyldiimide towards 1-aminocyclohexenes, leading to enamine derivatives bearing a cyclohexanespirotriazolidinone substituent is reported.

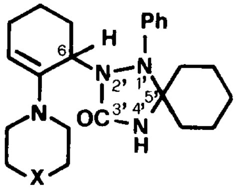
The reactivity of several asymmetric diimides with various conjugated cyclohexeneamines has been previously reported.[1-4] In particular, Ar-N=N-CO-Ar' was shown to furnish stable 1,3,4-oxadiazine derivatives 1.[1,2] As a continuation of our studies on heterocyclization reactions, it seemed of interest to examine the behaviour of Ph-N=N-$CONH_2$[5] towards the same substrates. Since α,β-unsaturated amides lead easily to bicyclic lactame systems[6,7] by reacting with enamines, the aforementioned diimide might, in principle, afford the corresponding bicyclic 1,2,4-triazin-3-one derivatives 2.



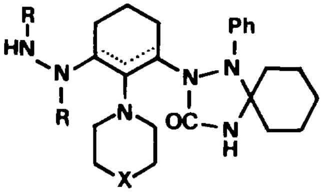
1



2



3a,b
a:X=O ; b:X=CH_2



4a,b
R=COOEt

In the present paper we wish to report the first results of this investigation. In contrast to our expectation, no 1:1 adducts were obtained when 1-(morpholin-4-yl)cyclohexene and phenylcarbamoyldiimide were allowed to react, although the reactions were carried out under a variety of conditions, *i.e.* at room temperature and at reflux by using benzene, acetonitrile, ethanol, and dioxane as solvents. Surprisingly, the reaction led to a crystalline compound m.p. 176-7° (from ethanol) which had a molecular weight of 399.5 (determined by osmometry in $CHCl_3$ solution) and a corresponding molecular formula $C_{23}H_{32}N_4O_2$ (elemental analysis). These data, together with the presence of 18H at high field (δ 2.75-0.9) in the ^{1}N NMR spectrum,[8] indicated that the starting enamine and diimide reacted in a 2:1 molar ratio; actually, when a twofold excess of 1-(morpholin-4-yl)cyclohexene was used, a double amount of the product was obtained.

Furthermore, the presence of a trisubstituted enamine moiety, suggested both by the ^{1}H NMR (δ 4.75) and IR (1645 cm^{-1}) spectra,[8] was chemically confirmed by the reaction with $EtO_2C{-}N{=}N{-}CO_2Et$[9] (in ethanol at room temperature for 48 hours), which furnished a 1:1 adduct in quantitative yield. Analogous results were obtained starting from 1-(piperidin-1-yl)cyclohexene. The spectral and chemical data, however, did not permit unambiguous structural assignments and consequently a single crystal of the compound m.p. 176-7° was subjected to X-ray crystallographic analysis. In this way product $C_{23}H_{32}N_4O_2$ proved to be 1-(morpholin-4-yl)-6-[cyclohexanespiro-5'-(1'-phenyl-triazolidin-3'-on)-2'-yl]-cyclohex-1-ene (3a) (Figure) (3b[8] for the piperidine derivative).

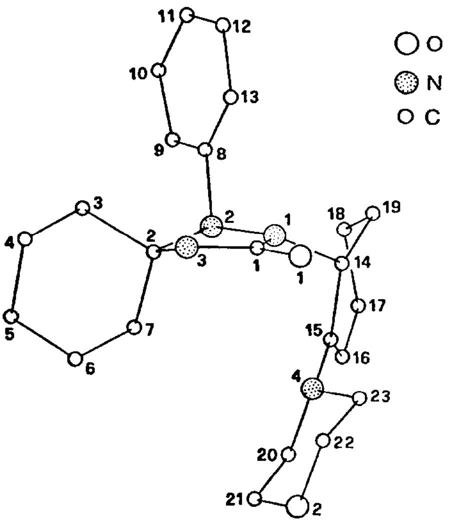


Figure : A view of 3a with the numbering of the atoms.

Well shaped colourless single crystals were obtained by slow evaporation from an ethanol solution. The crystal data are as follows: $C_{23}H_{32}N_4O_2$, MW = 396.5, monoclinic, space group $P2_1/n$, $a = 10.372(4)$, $b = 18.217(6)$, $c = 11.648(4)$ Å, $\beta = 90.8(1)°$, $U = 2200.7$ Å^3, $D_c = 1.21$ g cm^{-3}, $Z = 4$, $D_m = 1.20$ (by flotation). Intensities were collected on a Siemens difractometer by the θ-2θ scan technique in the range $3.5° \leqslant \theta \leqslant 27°$. A total of 1525 independent reflections with $I \geqslant 3\sigma(I)$ were used and corrected for Lorentz and polarization effect. The structure was solved by direct methods with the multiple-solution programme for the SHELX 76 System[10] using the normalized structure factors with $E \geqslant 1.3$ and was refined by the block diagonal least-squares method. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms. The hydrogen atoms were introduced at calculated positions (B = 5Å^2) but not refined. The weighting scheme was $w = 1/(A + |F_o| + B|F_o|^2)$, where A = 13.6 and B = 0.016 were chosen to maintain $w(|F_o| - |F_c|)^2$, essentially constant over all ranges of $|F_o|$ and $\sin\theta/\lambda$. The final R value was 0.038. Atomic scattering factors were those of Moore.[11] Atomic parameters, bond lengths, and bond angles are available elsewhere.[12]

In the light of the crystallographic results, the 1:1 adducts with diethoxy-carbonyldiimide were assigned structures 4a[8] and 4b[8].

The most striking feature of structures 3 is the cyclohexanespirotriazolidinone mojety, linked to the cyclohexenamine C-6 atoms through the N-2' atom. This linkage would indicate a regiochemistry opposite to that observed for Ar-N=N-CO-Ar',[1] provided that also the reactions with Ar-N=N-$CONH_2$ imply an initial electrophilic attack by the -N=N- group to the β-carbon atom of the 1-aminocyclohexenes.

Compounds 3 undergo a number of reactions which are being investigated at present. Studies are underway to elucidate the factors determining the unexpected behaviour of phenylcarbamoyldiimide towards enamines, as well as the mechanism of the reactions.

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[8] All new compounds gave satisfactory elemental analyses within ±0.4%
The ^1H NMR spectra were run at 60 MHz. Compounds 3 were obtained in the best yields (65-70%) when the reactions were carried out in anhydrous ethanol under reflux for 45 min. 3a, m.p. 176-7° (from EtOH); IR (Nujol), cm^{-1}: 3170 (NH), 1685 (CO), 1645 (N-C=C); ^1H NMR ($CDCl_3$), δ : 7.2 (m, 5H, C_6H_5), 6.9 (s,1H, NH), 4.75 (broad m, 2H, C=CH and CH-N-CO), 3.65 (m,4H, CH_2-O-CH_2), 3.1 (m, 2H, CH_2-N or CH-N-CH),[13] 2.75-0.9 (18H). 3b, m.p. 155-6° (from EtOH); IR (Nujol), cm^{-1}: 3160 (NH), 1690 (CO), 1640 (N-C=C); ^1H NMR ($CDCl_3$), δ : 7.35 (m, 5H, C_6H_5), 6.95 (s, 1H, NH), 4.85 (broad m, 2H, C=CH and CH-N-CO), 3.0 (m, 2H, CH_2N or CH-N-CH),[13] 2.5-1.0 (24H). 4a, m.p. 145-8° (flash chromatography); IR (Nujol), cm^{-1}: 3220 (NH), 1753, 1723 (CO_2Et), 1690 (CO), 1650 (N-C=C); ^1H NMR ($CDCl_3$), δ : 7.35 (m, 7H, C_6H_5 and NH), 4.7 (m, 1H, CH-N), 4.2 (q, 4H, CO_2CH_2), 3.7 (m, 4H, CH_2-O-CH_2), 3.1 (m, 2H, CH_2-N or CH-N-CH),[13] 2.8-0.7 (24H). 4b, m.p. 128-31° (flash chromatography); IR (Nujol), cm^{-1}:

3280, 3200 (NH), 1760, 1715 sh (CO_2Et), 1700 (CO), 1650 (N-C=C); ^1H NMR ($CDCl_3$), δ : 7.4 (m, 7H, C_6H_5 and NH), 4.6 (m, 1H, CH-N), 4.2 (q, 4H, CO_2CH_2), 3.1-0.75 (32H).

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[12] Supplementary material has been submitted for deposition at the Cambridge Crystallographic Data Centre.

[13] Two of the four protons adjacent to the nitrogen atoms in the amine rings are shifted upfield, very probably by the shielding of the heterocyclic carbonyl group.

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