# Heterocycles from Heterocycles. - III [1]. 1,3,5-Trisubstituted Hexahydro-1,3,5-triazines-2-ones from 1,3,5-Trisubstituted Hexahydro-1,3,5-triazines and Organic Isocyanates



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1,3,5-Trisubstituted hexahydro-1,3,5-triazin-2-ones **3** are easily obtained by the reaction of 1,3,5-trisubstituted hexahydro-1,3,5-triazines **1** with organic isocyanates **2**. The reaction is believed to occur by the sequential addition to **2** of two molecules of the monomeric *N*-methyleneamines in thermal equilibrium with **1**. Substituent scrambling at the operating temperature (120°) was negligible. The crystal structure of 1,3,5-triphenylhexahydro-1,3,5-triazin-2-one (**3a**) has been determined by X-ray diffraction methods.

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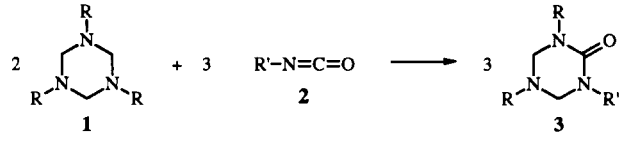
## Introduction.

Although the reaction between primary amines and formaldehyde is one of the oldest known in organic chemistry [2], only recently a systematic study of the mechanistic features as well as of the array, identification and chemical properties of the reaction products has been undertaken [3]. 1,3,5-Trisubstituted hexahydro-1,3,5-triazines **1**, the oligomeric form to which *N*-methyleneamines usually polymerize, are emerging as the stable source of the very reactive dimeric zwitterionic **4** [4] and monomeric species, both undergoing useful and interesting reactions, like addition of carboxylic anhydrides [3e,f], alkyl nitrites [5], acyl halides [1a], cyclization reactions [1b] and complex formation with transition metals [6].

Scheme A




## Results and Discussion.

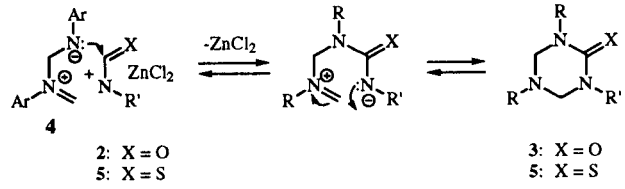
It was reported [7] that the zinc chloride catalyzed reaction between some *N*-trialkylhexahydro-1,3,5-triazines **1**, (R = Me, Pr, Bu, *t*-Bu) and some organic isocyanates **2**, (R' = Me, Pr, Bu, Ph) gave the corresponding 1,3,5-trisubstituted hexahydro-1,3,5-triazin-2-ones **3** in fair yields. Following our recent work [1b] about the cyclization of the dimeric form **4** of *N*-methyleneamines on organic isothiocyanates **5** to yield the corresponding sulfur derivatives **6**, we now wish to report the successful cyclization of **1** with **2** to produce **3** in fair to excellent yields without any catalyst (Table 1, Scheme A).

Table 1
1,3,5-Trisubstituted Hexahydro-1,3,5-triazin-2-ones **3** Prepared

| Triazine (R) | Isocyanate (R') | Yield (%) | mp (C°) | Recrystallization solvent(s) | | Reaction product (R) | (R') |
|---|---|---|---|---|---|---|---|
| **1a** ($C_6H_5$) | **2a** ($C_6H_5$) | 86 | 168 | Hex/$CH_2Cl_2$ | **3a** | $C_6H_5$ | $C_6H_5$ |
| **1d** (4-MeO-$C_6H_4$) | **2b** (4-MeO-$C_6H_4$) | 84 | 176 | Hex/$CH_2Cl_2$ | **3b** | 4-MeO-$C_6H_4$ | 4-MeO-$C_6H_4$ |
| **1e** (4-F-$C_6H_4$) | **2d** (4-F-$C_6H_4$) | 90 | 138 | Hex/AcOEt | **3c** | 4-F-$C_6H_4$ | 4-F-$C_6H_4$ |
| **1g** (4-Cl-$C_6H_4$) | **2e** (4-Cl-$C_6H_4$) | 86 | 161 | Hex/$CH_2Cl_2$ | **3d** | 4-Cl-$C_6H_4$ | 4-Cl-$C_6H_4$ |
| **1b** (4-Me-$C_6H_4$) | **2a** | 68 | 152 | Hex/$CH_2Cl_2$ | **3e** | 4-Me-$C_6H_4$ | $C_6H_5$ |
| **1e** | **2a** | 72 | 122 | Hex/$CH_2Cl_2$ | **3f** | 4-F-$C_6H_4$ | $C_6H_5$ |
| **1f** (3-Cl-$C_6H_4$) | **2a** | 70 | 140 | $Et_2O$ | **3g** | 3-Cl-$C_6H_4$ | $C_6H_5$ |
| **1g** (4-Cl-$C_6H_4$) | **2a** | 76 | 161 | Hex/$CH_2Cl_2$ | **3h** | 4-Cl-$C_6H_4$ | $C_6H_5$ |
| **1h** (4-Br-$C_6H_4$) | **2a** | 73 | 172 | *i*-PrOH | **3i** | 4-Br-$C_6H_4$ | $C_6H_5$ |
| **1a** | **2c** (4-$NO_2$-$C_6H_4$) | 70 | 166 | Hex/$CH_2Cl_2$ | **3j** | $C_6H_5$ | 4-$NO_2$-$C_6H_4$ |
| **1e** | **2e** | 86 | 142 | Hex/$CH_2Cl_2$ | **3k** | 4-F-$C_6H_4$ | 4-Cl-$C_6H_4$ |
| **1b** | **2d** | 73 | 153 | Hex/$CH_2Cl_2$ | **3l** | 4-Me-$C_6H_4$ | 4-F-$C_6H_4$ |
| **1b** | **2e** | 89 | 167 | Hex/$CH_2Cl_2$ | **3m** | 4-Me-$C_6H_4$ | 4-Cl-$C_6H_4$ |
| **1c** (4-*t*-Bu-$C_6H_4$) | **2e** | 75 | 155 | Hex/$CH_2Cl_2$ | **3n** | 4-*t*-Bu-$C_6H_4$ | 4-Cl-$C_6H_4$ |
| **1i** ($C_7H_7$) | **2a** | 85 | 74 | Hex/$CH_2Cl_2$ | **3o** | $C_7H_7$ | $C_6H_5$ |
| **1j** ($C_6H_{11}$) | **2a** | 70 | 132 | Cyclohexane | **3p** | $C_6H_{11}$ | $C_6H_5$ |
| **1j** | **2f** ($C_6H_{11}$) | 40 | 91 | Hexane | **3q** | $C_6H_{11}$ | $C_6H_{11}$ |
| **1a** | **2f** | traces | -- | -- | **3r** | $C_6H_5$ | $C_6H_{11}$ |

The reaction is carried out in the absence of solvent, with a slight excess of **2** during 20 hours at 120°; the advantage of not using an acidic catalyst is evident, when thought is given to the self-reactivity of **1** in the presence of these compounds [2]. The most reactive systems appeared to be those for which both R and R' were aromatic and those for which R was aliphatic and R' aromatic, but also bulky substituted partners, like in the case of R = R' = *c*-Hex, did provide the new heterocyclic system 1,3,5-tri(*c*-hexyl)hexahydro-1,3,5-triazin-2-one (**3q**). Only the combination R = aromatic, R' = aliphatic proved to be completely unreactive under our conditions, in line with the behaviour found for the sulfur counterpart. This may be rationalized by both looking at the decreased reactivity of the aromatic ylid **4** with respect to an aliphatic one, due to the partial spreading of the nitrogen negative charge on the aromatic ring, and the change of charge distribution at the carbon center of the cyanate **2** caused by the electron withdrawing aromatic ring with respect to an aliphatic substituent. Most likely, the function of a catalyst in these reactions is that of activating the thiocyanate by co-ordination with either heteroatoms, making the central carbon more positive, rather than breaking down **1** to the reactive form **4**. The cyclization itself may not be a fully concerted step (Scheme B).

Scheme B

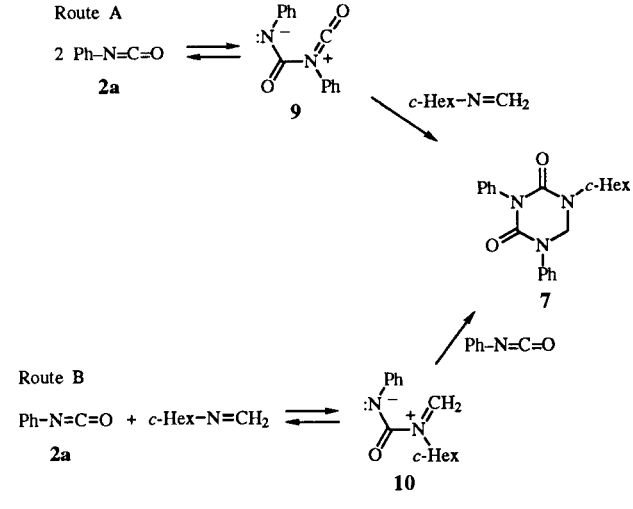



The reaction between **1** and **2** is highly irreversible under the present conditions. This fact leads to the important consequence that little, if any, substituent scrambling was observed, at variance with the case of sulfur derivatives **6** under similar conditions. If we accept the two step mechanistic picture for the formation of these adducts, for the principle of the microscopic reversibility the reverse pathway will account for their decomposition. But it can be argued that, due to the better delocalization in the oxygen system, all bonds might have a larger polar character leading to bond strengthening. Moreover, once the first, *e.g.* the N-$CH_2$, bond is broken, the second one will offer a much higher resistance to cleavage than in the sulfur analog, allowing time for the former to be reconstituted. Thus, both thermodynamics and kinetics would work against the retrocyclization reaction, the necessary step for substituent scrambling.

As expected polarity of the C=X bond is the key factor for the reactivity of these systems, reinforcing the hypothesis of the two step mechanism for cyclization. In fact, in a competitive experiment 1,3,5-triphenylhexahydro-1,3,5-triazine (**1a**) was allowed to react with equimolecular concentrations of phenyl isocyanate (**2a**) and phenyl isothiocyanate (**5a**): the product distribution was sharply (77% *vs* 23%) in favour of **3a**. Equally significant was the experiment in which **1a** and 1,3,5-tri(*c*-hexyl)hexahydro-1,3,5-triazine (**1j**) in equimolecular concentrations were allowed to compete for **2a**: the large prevalence (87% *vs* 13%) of the aliphatic-aromatic product 1,5-di(*c*-hexyl)-3-phenylhexahydro-1,3,5-triazin-2-one (**3p**) over the fully aromatic **3a** leads to the same conclusions. Not only scrambling, but even the simple isomerization of the compound with $R_2R'$ substituents was ruled out by $^1H$ nmr spectroscopy and electron impact ms.

Consistently with the pattern outlined above, when the reaction between **1j** and **2a** was carried out at higher temperature (150°) in the presence of a homogenizing, relatively polar solvent like 1,2-dichlorobenzene, ms analysis of the reaction mixture, after evaporation of volatile products *in vacuo* at 100°, revealed the formation of considerable amounts of scrambled products in addition to a completely new type of product incorporating a molecule of *N*-methylene-*c*-hexylamine and two of **2a**, namely 1,5-diphenyl-3-(*c*-hexyl)hexahydro-1,3,5-triazine-2,6-dione (**7**). Two possible routes may be envisaged for its formation. Isocyanates **2** are known [8] to trimerize to 1,3,5-trisubstituted hexahydrotriazine-2,4,6-triones **8**, the zwitterionic dimer **9** being necessarily a reaction intermediate. Indeed, the slower decomposition of **1j** to the reactive dimer **4** gave time to **2a** for self-addition to yield substantial concentrations of 1,3,5-triphenylhexahydrotriazine-2,4,6-trione (**8a**). Moreover, the highly reactive 4-nitrophenyl isocyanate (**2c**) underwent practically only self condensation in the interaction with **1a**, in contrast to any reasonable expectation.

In these cases our trimers only fulfilled the function of amine catalysts [8] for the trimerization of **2**. Thus, in an amine catalyzed or spontaneous dimerization, **2a** would dimerize (route A) and the formed dimer **9** eventually



picked up a reactive polar molecule of *N*-methylene-*c*-hexylamine (**4j**), whose concentration is expected to increase with temperature. The other route (B) envisages a preliminary formation of adduct **10**, made up by the interaction of one molecule of **2a** and one of **4j**, eventually reacting with **2a** to yield **7**.

Other products identified in the mixture from the reaction between **1j** and **2a** were: 1,5-diphenyl-3-(*c*-hexyl)-hexahydro-1,3,5-triazine-2-one (**3r**) (m/z = 335) or its isomer 1,3-diphenyl-5-(*c*-hexyl)hexahydro-1,3,5-triazine-2-one (**3r'**) (m/z = 335), 1,5-di(*c*-hexyl)-3-phenylhexahydro-1,3,5-triazin-2-one (**3p**) (m/z = 341) or its isomer 1,3-di(*c*-hexyl)-5-phenylhexahydro-1,3,5-triazin-2-one (**3p'**) (m/z = 341), **3a** and **8a**.

The role of the amine in the trimerization of **2a** was made evident by the much lower conversion observed in the presence of the less basic amine **1a** than **1j** .

A paper [9] has reported the reaction of some dichlorophenyl isocyanates with both 1,3,5-trimethyl and 1,3,5-triethylhexahydro-1,3,5-triazine which were found to yield the corresponding triazin-2-ones and that of methyl isocyanate with the former triazine which gave a 1,3,5-trimethylhexahydro-1,3,5-triazin-2-one in unspecified yields. The authors seem to assume the formation of bicyclic adducts between two molecules of the isocyanate and three molecules of monomeric *N*-methyleneamine as the possible intermediates to the observed final products, but we did not find any evidence yet in favour of this hypothesis.

The carbonyl stretching band (Table 2) in the ir spectra of compounds **3** is located between 1630 and 1670 $cm^{-1}$ and is of great intensity. This should be compared with a ν (C=O) value of 1620 $cm^{-1}$ for *N,N'*-di(*c*-hexyl)urea (**11**) and 1640 $cm^{-1}$ for *N,N'*-diphenylurea (**12**). Ring formation seems therefore to cause a hypsochromic shift.

In agreement with an average symmetrical structure on either sides of a plane bisecting the plane of the urea function at right angle in solution, compounds **3** with a single substituent type show a single sharp singlet for the two

Table 2

Properties of 1,3,5-Trisubstituted Hexahydrotriazin-2-ones **3a-q** Isolated

| Compound | ir [a] (ν, ppm; J, Hz) | $^1$H nmr [b] (δ, ppm) | $^{13}$C nmr [b] (δ, ppm) | ms (m/z, rel %) | | Analysis Calcd. | Found |
|---|---|---|---|---|---|---|---|
| **3a** $C_{21}H_{19}N_3O$ | 1640, 1590, 1475, 1440, 1400, 1295, 1205, 1175, 795, 765, 750, 730, 690 | 5.23 (4H, *s*), 7.02-7.40 (15H, m) | 68.1, 119.0, 123.0, 125.8, 125.9, 128.8, 129.5, 141.0, 146.9, 153.1 (C=O) | 329 ($M^+$, 5), 119 (5), 106 (14), 105 (100), 104 (31), 77 (21), 51 (7) | C<br>H<br>N | 76.57<br>5.81<br>12.76 | 76.62<br>5.82<br>12.71 |
| **3b** $C_{24}H_{25}N_3O_4$ | 1645, 1600, 1505, 1475, 1445, 1395, 1290, 1240, 1180, 1025, 830, 795 | 3.76 (6H, *s*), 3.78 (3H, *s*), 5.09 (4H, *s*), 6.84 (4H, pseudo d, J = 9), 7.12 (2H, pseudo d, J = 9), 7.14 (4H, pseudo d, J = 9) | 55.4, 55.4, 69.3, 114.1, 114.6, 121.2, 127.3, 134.0, 140.8, 153.7, 155.7, 157.5 (C=O) | 419 ($M^+$, 1), 149 (10), 135 (100), 120 (29), 92 (5), 77 (3), 65 (5) | C<br>H<br>N | 68.72<br>6.01<br>10.02 | 68.73<br>6.02<br>12.03 |
| **3c** $C_{21}H_{16}N_3OF_3$ | 1640, 1500, 1470, 1440, 1330, 1295, 1215, 1195, 1020, 825, 810, 790, 740, 525 | 5.14 (4H, *s*), 6.95-7.25 (12H, m) | 69.0, 121.1, 121.3, 127.6, 127.7, 136.7, 136.7, 143.2, 143.3, 153.3 (C=O) | 383 ($M^+$, 3), 124 (21), 123 (100), 109 (8), 95 (32), 82 (3), 57 (3) | C<br>H<br>N | 65.79<br>4.21<br>10.96 | 65.78<br>4.20<br>10.97 |
| **3d** $C_{21}H_{16}N_3OCl_3$ | 1640, 1615, 1480, 1465, 1435, 1280, 1195, 1165, 1080, 820, 800, 755, 730 | 5.33 (4H, *s*), 7.12-7.55 (12H, m) [c] | 66.4, 119.7, 125.8, 127.3, 128.5, 129.1, 129.6, 140.0, 145.4, 152.3 (C=O) [c] | 437 ($M^+$, 0.1), 435 ($M^+$, 0.2), 433 ($M^+$, 1), 431 ($M^+$, 1), 153 (10), 141 (54), 139 (100), 133 (40), 111 (20), 75 (10) | C<br>H<br>N | 58.29<br>3.73<br>9.71 | 58.40<br>3.74<br>9.70 |
| **3e** $C_{23}H_{23}N_3O$ | 1665, 1500, 1460, 1430, 1290, 1250, 1200, 1170, 1030, 810, 760, 735, 690 | 2.30 (3H, *s*), 2.31 (3H, *s*), 5.17 (2H, *s*), 5.20 (2H, *s*), 7.00-7.37 (13H, m) | 20.6, 20.9, 68.4, 68.5, 119.3, 125.7, 125.8, 128.8, 129.5, 130.0, 132.5, 135.4, 135.7, 138.4, 141.2, 144.6, 153.2 (C=O) | 357 ($M^+$, 7), 238 (4), 133 (6), 120 (16), 119 (100), 106 (11), 105 (82), 91 (49), 77 (16), 65 (12) | C<br>H<br>N | 77.28<br>6.48<br>11.75 | 77.20<br>6.49<br>11.76 |
| **3f** $C_{21}H_{17}N_3OF_2$ | 1640, 1590, 1500, 1470, 1445, 1305, 1220, 1200, 1180, 825, 760, 695 | 5.15 (2H, *s*), 5.19 (2H, *s*), 6.95-7.42 (13H, m) | 68.8, 69.2, 121.1, 121.3, 125.7, 126.1, 127.6, 127.8, 128.9, 136.7, 136.8, 140.7, 143.2, 143.3, 153.1 (C=O) | 365 ($M^+$, 3), 242 (2), 123 (86), 122 (31), 105 (100), 104 (18), 95 (18), 77 (12), 75 (5), 51 (5) | C<br>H<br>N | 69.03<br>4.69<br>11.50 | 69.10<br>4.69<br>11.48 |
| **3g** $C_{21}H_{17}N_3OCl_2$ | 1635, 1480, 1470, 1435, 1390, 1290, 1245, 1205, 1170, 1080, 995, 835, 810, 745, 735, 690 | 5.18 (2H, *s*), 5.20 (2H, *s*), 6.85-7.07 (5H, m), 7.14-7.42 (8H, m) | 68.1, 68.2, 120.5, 125.9, 126.4, 126.8, 128.4, 129.0, 129.1, 129.6, 131.4, 139.4, 140.6, 145.4, 152.8 (C=O) | 401 ($M^+$, 0.1), 399 ($M^+$, 0.6), 397 ($M^+$, 1), 153 (3), 141 (16), 111 (18), 106 (7), 105 (100), 77 (10) | C<br>H<br>N | 63.33<br>4.30<br>10.55 | 63.32<br>4.29<br>10.56 |
| **3h** $C_{21}H_{17}N_3OCl_2$ | 1635, 1580, 1480, 1470, 1440, 1390, 1290, 1205, 1170, 1030, 995, 810, 745, 735, 690 | 5.29 (4H, *s*), 7.04-7.43 (13H, m) [c] | 67.1, 67.3, 119.9, 125.8, 126.8, 127.0, 128.5, 128.6, 129.2, 130.2, 139.9, 141.0, 145.4, 145.5, 152.5 (C=O) [c] | 401 ($M^+$, 0.2) 399 ($M^+$, 2), 397 ($M^+$, 3), 258 (2), 153 (7), 141 (35), 139 (90), 111 (19), 106 (18), 105 (100), 77 (25), 51 (12) | C<br>H<br>N | 63.33<br>4.30<br>10.55 | 63.23<br>4.30<br>10.56 |

Table 2 (continued)

| Compound | ir [a] (ν, ppm; J, Hz) | $^1$H nmr [b] (δ, ppm) | $^{13}$C nmr [b] (δ, ppm) | ms (m/z, rel %) | Analysis | Calcd. | Found |
|---|---|---|---|---|---|---|---|
| **3i** $C_{21}H_{17}N_3OBr_2$ | 1630, 1470, 1435, 1380, 1290, 1240, 1200, 1170, 990, 830, 805, 730 | 5.31 (2H, s), 5.33 (2H, s), 7.10-7.55 (13H, m) [c] | 66.1, 66.5, 113.6, 117.6, 120.1, 125.6, 125.8, 127.4, 128.6, 131.3, 132.0, 140.6, 141.1, 145.9, 152.3 (C=O) [c] | 489 (M$^+$, 0.1), 487 (M$^+$, 0.3), 485 (M$^+$, 0.1), 185 (29), 184 (10), 183 (31), 105 (100), 104 (14), 77 (14), 51 (7) | C<br>H<br>N | 51.77<br>3.52<br>8.62 | 51.75<br>3.52<br>8.61 |
| **3j** $C_{21}H_{18}N_4O_3$ | 1670, 1595, 1495, 1460, 1435, 1350, 1290, 1265, 1210, 1170, 1110, 750, 695 | 5.24 (2H, s), 5.34 (2H, s), 7.00-7.52 (12H, m), 8.17 (2H, pseudo d, J = 9.2) | 67.4, 68.5, 119.0, 123.5, 124.0, 124.2, 126.3, 126.8, 129.2, 129.7, 140.3, 144.1, 146.3, 147.2, 152.5 (C=O) | 374 (M$^+$, 4), 150 (30), 134 (5), 119 (14), 106 (18), 105 (100), 104 (39), 77 (30), 51 (10) | C<br>H<br>N | 67.37<br>4.85<br>14.96 | 67.30<br>4.86<br>14.95 |
| **3k** $C_{21}H_{16}N_3OF_2Cl$ | 1645, 1505, 1490, 1470, 1445, 1300, 1220, 1200, 1185, 830 | 5.22 (2H, s), 5.25 (2H, s), 7.00-7.39 (12H, m ) [c] | 67.7, 68.1, 119.6, 120.3, 126.9, 127.7, 127.9, 128.5, 130.2, 137.0, 137.1, 139.9, 143.0, 143.1, 152.7 (C=O) [c] | 401 (M$^+$, 0.3), 399 (M$^+$, 1), 141 (13), 139 (42), 124 (10), 123 (100), 122 (28), 95 (16), 75 (6) | C<br>H<br>N | 63.08<br>4.03<br>10.51 | 63.10<br>4.04<br>10.53 |
| **3l** $C_{23}H_{22}N_3OF$ | 1665, 1505, 1435, 1400, 1290, 1260, 1225, 1205, 1155, 815, 785, 740 | 2.31 (3H, s), 2.32 (3H, s), 5.16 (4H, s), 6.95-7.25 (12H, m) | 20.6, 20.9, 68.4, 68.7, 119.2, 125.8, 127.6, 127.7, 129.5, 130.1, 132.6, 135.8, 137.1, 137.2, 138.3, 144.5, 153.3 (C=O) | 375 (M$^+$, 10), 256 (3), 137 (6), 133 (14), 123 (75), 120 (24), 119 (100), 118 (50), 91 (66), 65 (19) | C<br>H<br>N | 73.58<br>5.91<br>11.19 | 73.59<br>5.90<br>11.20 |
| **3m** $C_{23}H_{22}N_3OCl$ | 1665, 1510, 1490, 1465, 1435, 1400, 1290, 1200, 1160, 815 | 2.30 (3H, s), 2.32 (3H, s), 5.15 (4H, s), 6.95-7.32 (12H, m) | 20.6, 20.9, 68.2, 68.5, 119.2, 125.9, 126.9, 128.8, 129.6, 130.0, 130.9, 132.6, 135.9, 138.2, 139.8, 144.3, 153.1 (C=O) | 393 (M$^+$, 0.3), 391 (M$^+$, 1), 153 (4), 139 (26), 119 (100), 118 (19), 91 (30), 77 (3), 63 (3) | C<br>H<br>N | 70.49<br>5.66<br>10.72 | 70.53<br>5.66<br>10.70 |
| **3n** $C_{29}H_{34}N_3OCl$ | 2920, 1645, 1485, 1425, 1390, 1280, 1260, 1160, 830 | 1.29 (9H, s), 1.31 (9H, s), 5.20 (4H, s), 7.02-7.40 (12H, m) | 31.3, 31.4, 34.2, 34.5, 68.2, 68.4, 118.8, 125.5, 125.9, 126.4, 126.8, 128.8, 131.0, 138.0, 139.8, 144.2, 146.0, 149.1, 153.2 (C=O) | 477 (M$^+$, 0.3), 475 (M$^+$, 1), 162 (12), 161 (100), 153 (11), 146 (98), 139 (41), 118 (14), 106 (6), 77 (7) | C<br>H<br>N | 73.17<br>7.20<br>8.83 | 73.02<br>7.21<br>8.85 |
| **3o** $C_{23}H_{23}N_3O$ | 1625, 1485, 1470, 1440, 1300, 1245, 1220, 1170, 1140, 1120, 780, 750, 730, 695, 685 | 3.89 (2H, s), 4.21 (2H, s), 4.54 (2H, s), 4.60 (2H, s), 7.05-7.40 (15H, m) | 48.4, 55.1, 65.4, 69.2, 125.6, 125.8, 127.5, 127.6, 128.5, 128.6, 128.7, 128.9, 129.1, 137.2, 138.2, 142.0, 154.3 (C=O) | 357 (M$^+$, 2), 238 (9), 119 (55), 105 (10), 92 (14), 91 (100), 77 (6), 65 (8) | C<br>H<br>N | 77.28<br>6.48<br>11.75 | 77.31<br>6.47<br>11.72 |
| **3p** $C_{21}H_{31}N_3O$ | 2890, 2820, 1630, 1470, 1440, 1400, 1300, 1275, 1245, 1165, 1130, 800, 760, 740, 690 | 1.05-2.00 (20H, m), 2.75-2.95 (1H, m), 4.20-4.35 (1H, m), 4.40 (2H, s), 4.65 (2H, s), 7.15-7.40 (5H, m) | 25.1, 25.6, 25.7, 25.9, 30.5, 31.3, 52.1, 55.4, 59.4, 65.5, 125.1, 125.4, 128.6, 142.2, 154.1 (C=O) | 341 (M$^+$, 11), 230 (50), 119 (32), 111 (90), 105 (35), 83 (42), 82 (100), 68 (65), 55 (71) | C<br>H<br>N | 73.86<br>9.15<br>12.30 | 73.90<br>9.15<br>12.29 |
| **3q** $C_{21}H_{37}N_3O$ | 2880, 2820, 1635, 1475, 1440, 1270, 1175, 1125, 885, 805, 795, 755 | 1.05-2.05 (30H, m), 2.62-2.85 (1H, m), 4.28-4.70 (6H, m) | 25.1, 25.7, 25.8, 26.0, 30.7, 31.1, 52.2, 54.7, 58.2, 154.9 (C=O) | 347 (M$^+$, 22), 346 (48), 264 (19), 236 (10), 221 (11), 155 (16), 125 (35), 112 (96), 82 (100), 55 (99) | C<br>H<br>N | 72.57<br>10.73<br>12.09 | 72.50<br>10.75<br>12.10 |

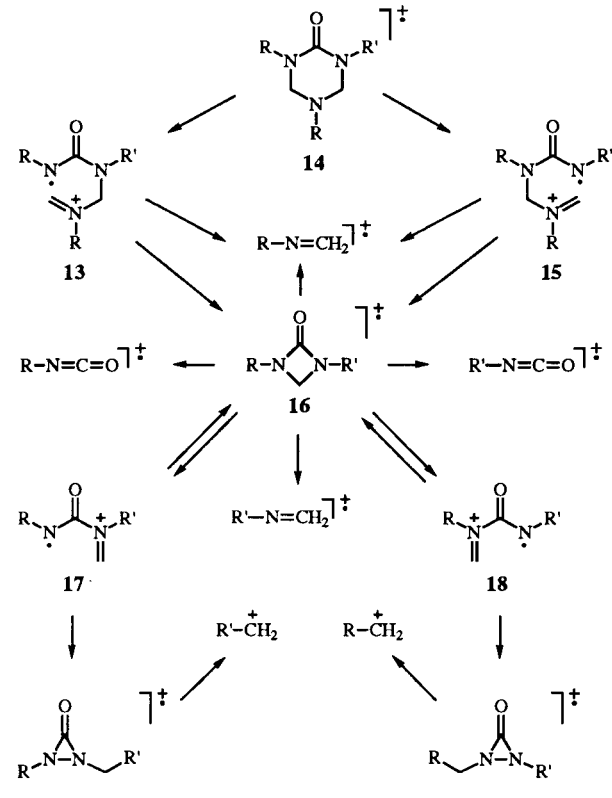
[a] Spectra were recorded in potassium bromide. [b] Spectra recorded in deuteriochloroform using tetramethylsilane as the internal standard. [c] Spectra recorded in dimethyl sulfoxide-$d_6$ solution using tetramethylsilane as the internal standard.

methylene groups in the $^1$H nmr spectrum. The two locations are respectively in the ranges 5.09-5.35 ppm (aromatic or semiaromatic urea functions in the ring) or 4.40-4.65 ppm (fully aliphatic substituent for the ring urea function) and in the narrow interval 65-69 ppm for all the compounds prepared. The methylene peaks are usually two, whenever the two substituents on the ring urea function are different, but no interaction between them could be inferred from the spectra. The $^{13}$C carbonyl resonance seemed little influenced by the substituents and is to be found in the range 152-157 ppm: this appeared, as expected, the most affected nmr parameter when the oxygen is substituted for a sulfur in the ring backbone.

The 70 eV electron impact positive ion spectra of **3** all show the characteristics collected in Scheme 1, most of which are supported by metastable transitions; they repeat quite closely the corresponding behaviour of their sulfur analogs. The parent ions **13**, **14** and **15** of **3** are discernible, but of very minor intensity, as well as the ions derived by the loss of $RNCH_2$. The primary elimination of $RNCH_2$ from the parent ion is by far the preferred route of decomposition in most cases; an exception to this general behaviour was offered by 1,3-di(3-chlorophenyl)-5-phenylhexahydro-1,3,5-triazin-2-one (**3g**) which exhibited the ion at m/z 105

($PhN=CH_2^+$) as the base peak. The overwhelming propensity of formation of the ion at m/z 119 ($PhCH_2N=CH_2^+$) from the secondary ion **16** at m/z 238, derived from the parent ion of 1,3-dibenzyl-5-phenylhexahydro-1,3,5-triazin-2-one (**3o**), in addition to its primary decomposition origin, makes it by far the dominating feature of the spectrum of **3o**. Of course, the fully aliphatic 1,3,5-tri(*c*-hexyl)-hexahydro-1,3,5-triazin-2-one (**3q**) showed a more complicated pattern with additional peaks, like $M^+$ - H at m/z 346, $M^+$ - *c*-hex at m/z 264, superimposed to the general pattern. The aromatic compounds **3** all featured a minor, but interesting, rearrangement-cleavage, yielding the $RCH_2^+$ and $R'CH_2^+$ peaks of definitively minor intensity, once more analogously to their sulfur counterparts. As expected, the volatility of **3** is always very low, a fact reflected in the high solid probe temperatures, usually above 150° and, more significant, above their melting point, necessary to evaporate them into the ion source. This cast a doubt, whether what we have really observed is the result of the ionization of thermal fragments or the actual decomposition pattern of the parent ions of **3**. Although we did not collect the evidence that the former hypothesis can be ruled out altogether and for all **3**, we may notice that: 1) parent ions, although most often of low intensity, were always observed and many peaks were experimentally referred to them or to the intermediate **16** by the observation of metastable ions; 2) decomposition should have formed four molecules RNCO, R'NCO, $RNCH_2$ and $R'NCH_2$, everyone equally amenable to ionization at 70 eV. But the intensity ratio observed for the corresponding ions were consistently grossly at variance with the quite similar ones expected in the case of a predominant thermal decomposition. For a few compounds **3**, we proved their thermal stability above their melting points.

Scheme 1



From the synthetic viewpoint, it should be stressed that systems having this framework and the three substituents of the types here illustrated are for the most part new, as well as their facile approach here described [10].

There have been previous reports about the reaction between *N*-methyleneanilines oligomers and phenyl iso-

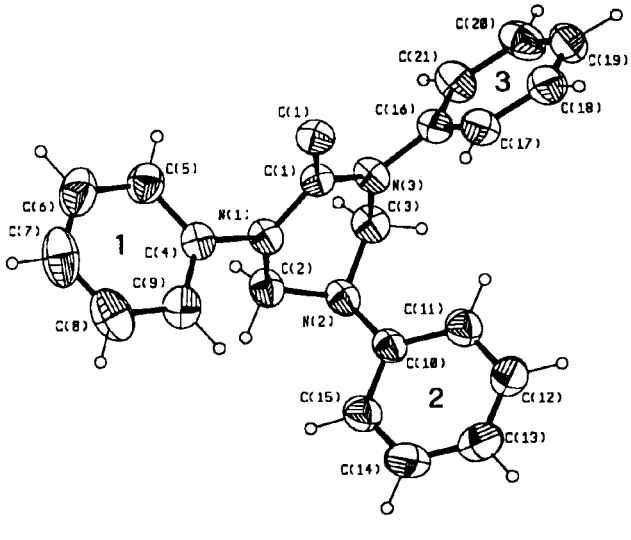



Figure 1. ORTEP view of 1,3,5-triphenylhexahydro-1,3,5-triazin-2-one (**3a**) with the atomic numbering scheme.

Table 3

Selected Bond Lengths (Å) and Angles for 1,3,5-Triphenylhexahydro-1,3,5-triazin-2-one (**3a**)

Bond Lengths (Å)

| | | | |
|---|---|---|---|
| O(1)-C(1) | 1.223(3) | N(1)-C(1) | 1.374(3) |
| N(1)-C(2) | 1.484(3) | N(1)-C(4) | 1.434(4) |
| N(2)-C(2) | 1.450(5) | N(2)-C(3) | 1.438(3) |
| N(2)-C(10) | 1.419(5) | N(3)-C(1) | 1.370(4) |
| N(3)-C(3) | 1.480(4) | N(3)-C(16) | 1.428(3) |

Bond Angles (°)

| | | | |
|---|---|---|---|
| C(2)-N(1)-C(4) | 114.8(2) | C(1)-N(1)-C(4) | 121.5(2) |
| C(1)-N(1)-C(2) | 122.5(2) | C(3)-N(2)-C(10) | 118.4(3) |
| C(2)-N(2)-C(10) | 116.1(3) | C(2)-N(2)-C(3) | 106.9(2) |
| C(3)-N(3)-C(16) | 116.3(2) | C(1)-N(3)-C(16) | 121.9(2) |
| C(1)-N(3)-C(3) | 121.6(2) | N(1)-C(1)-N(3) | 115.6(2) |
| O(1)-C(1)-N(3) | 122.4(3) | O(1)-C(1)-N(1) | 121.9(3) |
| N(1)-C(2)-N(2) | 110.1(2) | N(2)-C(3)-N(3) | 110.3(2) |
| N(2)-C(10)-C(15) | 119.9(3) | N(2)-C(10)-C(11) | 122.3(3) |
| N(1)-C(4)-C(5) | 120.9(3) | N(1)-C(4)-C(9) | 119.3(3) |
| N(3)-C(16)-C(21) | 118.6(3) | N(3)-C(16)-C(17) | 121.8(3) |

Table 4

Atomic Coordinates and U Equivalent ($Å^2 \times 10^3$) with Esd's in Parentheses for 1,3,5-Triphenylhexahydro-1,3,5-triazin-2-one (**3a**)

| Atom | x | y | z | Ueq [a] | Atom | x | y | z | Ueq [a] |
|---|---|---|---|---|---|---|---|---|---|
| O(1) | .29748(9) | .02155(9) | .5246(1) | 58(1) | C(4) | .1591(1) | -.0745(1) | .5466(2) | 53(1) |
| N(1) | .2028(1) | -.0788(1) | .4919(1) | 55(1) | C(9) | .1276(2) | -.1265(2) | .5975(2) | 72(2) |
| N(2) | .2164(1) | -.1499(1) | .4024(1) | 55(1) | C(8) | .0798(2) | -.1266(3) | .6458(2) | 93(2) |
| N(3) | .3013(1) | -.0316(1) | .4198(1) | 54(1) | C(7) | .0645(2) | -.0751(3) | .6441(2) | 102(3) |
| C(1) | .2691(1) | -.0262(1) | .4812(2) | 49(1) | C(6) | .0970(2) | -.0230(2) | .5944(3) | 93(2) |
| C(2) | .1671(1) | -.1362(1) | .4388(2) | 61(1) | C(5) | .1440(1) | -.0218(2) | .5451(2) | 69(2) |
| C(3) | .2648(1) | -.0875(1) | .3657(2) | 62(2) | C(16) | .3731(1) | .0133(1) | .4073(2) | 54(2) |
| C(10) | .2421(1) | -.1853(1) | .4445(2) | 55(1) | C(17) | .4216(1) | .0231(1) | .4595(2) | 66(2) |
| C(11) | .3110(2) | -.1669(2) | .4439(2) | 70(2) | C(18) | .4908(2) | .0604(2) | .4428(3) | 83(2) |
| C(12) | .3341(2) | -.2041(2) | .4831(2) | 86(2) | C(19) | .5117(2) | .0879(2) | .3739(3) | 87(2) |
| C(13) | .2894(2) | -.2595(2) | .5234(2) | 97(2) | C(20) | .4634(2) | .0791(2) | .3221(2) | 86(2) |
| C(14) | .2213(2) | -.2785(2) | .5242(2) | 92(2) | C(21) | .3944(2) | .0423(2) | .3386(2) | 71(2) |
| C(15) | .1972(2) | -.2430(2) | .4845(2) | 71(2) | | | | | |

[a] U equivalent is defined as one third of the trace of the orthogonalized Uij tensor.

cyanate (**2a**). The then believed *N*-methyleneaniline dimer, formulated as four membered ring compound, was described to yield 1,3-diaryl-2-oxo-1,3-diazacyclobutane, mp 222°, upon treatment with **2a** [11]. Later, the analogous "dimer" from 4-toluidine-formaldehyde condensation was reported to yield a compound, mp 148°, by reaction with **2a** [10].

Structure of 1,3,5-Triphenylhexahydro-1,3,5-triazin-2-one (**3a**).

The crystal is formed of well separated molecules. An ORTEP view of the asymmetric unit is shown in Figure 1 with the labelling scheme.

Selected bond distances and angles are reported in Table 3.

The central molecular core is formed by the heterocyclic ring present in an about *sofa* conformation with the N(2) atom as apex (the local symmetry of the ring is about a mirror), whereas it was chair in the parent compound 1,3,5-triphenylhexahydro-1,3,5-triazine [3a]. The presence of the C=O group induces not only a more planar shape of the heterocyclic ring with consequent conformational changes as already found in 1,4-di(4-methoxyphenyl)-3-phenylhexahydrotriazin-2-thione [1b] and 1,5-di(*c*-hexyl)-3-ethylhexahydrotriazin-2-thione [1b] (where the function of the oxygen is given by the sulphur), but also causes a reduction in the overall molecular symmetry. In fact, the crystallographic mirror plane present in the 1,3,5-triphenylhexahydro-1,3,5-triazine [3a] is absent here. Important differences concern also the bond distances C(1)-N(1) and C(1)-N(3) (involving the carbonyl carbon) which show the two comparable values of 1.374(3) and 1.370(4) Å, respectively, being significantly shorter of about 0.09 Å than the corresponding in the previously quoted derivative [3a] and suggesting the presence of partial electron delocalization for the N-CO-N system.

The same situation was present in the thione derivative [1b] where the analogous distances were, on average, 1.359(5) Å. In contrast, the adjacent N(1)-C(2) and N(3)-C(3) bonds (1.484(3) and 1.480(3) Å, respectively) are longer than expected, whereas, in the absence of the oxygen, the N-C bond distances in the heterocyclic ring are of the same order of magnitude (the range is from 1.446(3) to 1.463(3) Å).

The N-C (phenyl) bond distances vary from 1.419(5) to 1.434(4) Å and, with the exception of those adjacent to the C=O group, are shorter than the heterocyclic ones, as already found in 1,3,5-triphenylhexahydro-1,3,5-triazine [3a]. The values of dihedral angles between the phenyl groups 1^2 42.3(1)°, 2^3 36.0(1)° and 1^3 66.9(1)° reflect clearly the influence of the carbonyl oxygen, being the angle between the two rings facing the oxygen more open: 66.9(1)°.

## EXPERIMENTAL

Materials.

Isocyanates **2a-f** were commercially available (Aldrich, Milano, Italy); 1,3,5-trisubstituted hexahydro-1,3,5-triazines **1a-j** were prepared according to the amine-paraformaldehyde method [3a,g,12].

Equipment.

High pressure liquid chromatography analyses were performed with a Waters Millipore instrument, equipped with reverse phase $C_{18}$ Bondapak column (lengh 30 cm, i.d. 3.9 mm) and a fixed wavelength (254 nm) uv detector. Water/acetonitrile mixtures were found suitable for our analyses, operating at a flow rate of *ca.* 1 ml/minute. The ir spectra were recorded with a Jasco Model DS-702G spectrophotometer by the potassium bromide pellet technique. Electron impact (70 eV) mass spectra were obtained from a Finnigan 1020 apparatus. The $^1H$ and $^{13}C$ nmr data were secured from a Bruker Model AC-F 200 spectrometer. Only the most intense peaks beside the parent ion are reported from the mass spectra of new derivatives and location of only the strongest peaks is reported from the ir spectra (Table 2).

Crystallographic Measurements.

Crystal data for **3a**, $C_{21}H_{19}N_3O$, $M$ = 329.40, trigonal, space group *P3*, $a$ = 22.454(4), $c$ = 18.206(3) Å, $\gamma$ = 120°, $V$ = 7949(2) Å$^3$, $Z$ = 18, $D_x$ = 1.238 g cm$^{-3}$, F(000) 3132, $\mu$ = 0.73 cm$^{-1}$ for Mo-$K_\alpha$ radiation, $\lambda$ = 0.71069 Å. Suitable crystals were obtained by crystallization from ethanol. Unit cell and intensity data were obtained by using a Philips PW 1100 difractometer (Febo System). Reflections were measured at 294 K by the $\Theta/2\Theta$ scan method with a scan speed of 1.80° min$^{-1}$ and scan width 1.20°. Background counts at both ends of the scan 20 s. Because of the low absorption coefficients, no absorption corrections were applied to the intensity data. The structure was solved by direct methods with the SHELX 86 program [13]. Hydrogen atoms were introduced at the idealized positions ($d_{c\text{-}x}$ fixed at 0.98 Å) with a unique thermal factor ($U$ = 0.07 Å) . Non-hydrogen atoms were refined anisotropically. The final Fourier difference maps showed no significant peaks. The shift/error ratio in the final refinement was less than 0.01. Final $R$ = 0.035 $R_w$ = 0.040 with $w = [\sigma^2(F_o) + 0.000675F_o^2]^{-1}$. Calculations were performed using SHELX 76 [14]. Atomic scattering factors were taken from ref [15]. ORTEP program was used for drawings [16]. Final positional parameters for compound **3a** are given in Table 4.

Additional material available from the Cambridge Crystallographic Data Center comprises the hydrogen atomic coordinates, thermal parameters and remaining bond lengths and angles.

General Procedure for the Reaction of 1,3,5-Trisubstituted Hexahydro-1,3,5-triazines **1a-j** with Organic Isocyanates **2a-f**.

A mixture of **1** (4.0 mmoles) and **2** (8.0 mmoles) was kept at 120° during 24 hours in an atmosphere of dry argon under continuous stirring; any volatile material was then distilled off *in vacuo*. The reaction was preliminarily monitored by hplc and the solid residue was analyzed by complete evaporation of a tiny sample into the ion source of a mass spectrometer. Recrystallization from suitable solvents allowed us to obtain pure products in many instances. Data on the reactions and isolated compounds are collected in Table 1.

Reaction Between 1,3,5-Tri(*c*-hexyl)hexahydro-1,3,5-triazine (**1j**) and Phenyl Isocyanate (**2a**) in 1,2-Dichlorobenzene.

A mixture of **1j** (0.76 g, 2.0 mmoles), **2a** (0.71 g, 0.65 ml, 6.0 mmoles) and 1,2-dichlorobenzene (0.5 ml) was heated at 150° during 20 hours under an inert atmosphere with efficient stirring. Ms Analysis (ms) of the reaction mixture after evaporation of the volatile products *in vacuo* revealed the formation of **7**, together with considerable amounts of the following scrambled products: **3r**, **3r'**, **3p**, **3p'** and **3a**.

Competition Experiments.

a) A mixture of **1a** (0.10 g, 0.32 mmole), **2a** (0.11 g, 0.10 ml, 0.95 mmole) and **5a** (0.13 g, 0.11 ml, 0.95 mmole) was kept during 20 hours at 120° with stirring under an inert atmosphere. Unreacted **2a** and **5a** were then distilled off under reduced pressure and the residue, redissolved with acetonitrile, was analyzed by hplc (water/acetonitrile 50/50 vol/vol) for the content of **3a** (77%) and **6a** (23%), using the calibration factor obtained from the quantitative analysis of mixtures of an authentic specimen. b) A homogeneous solution of **1a** (0.53 g, 1.69 mmoles), **1j** (0.56 g, 1.69 mmoles) and **2a** (0.05 g, 0.04 ml, 0.40 mmole) kept under argon at 120° during 20 hours was then analyzed after cooling and addition of acetonitrile by hplc (water/acetonitrile 50/50 vol/vol) for the contents of **3p** (87%) and **3a** (13%), using a suitable calibration factor obtained from quantitative analysis of mixtures of known amounts of the authentic materials.

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