The Reaction of Phenyl Isocyanate with Dimethylacetamide (1)

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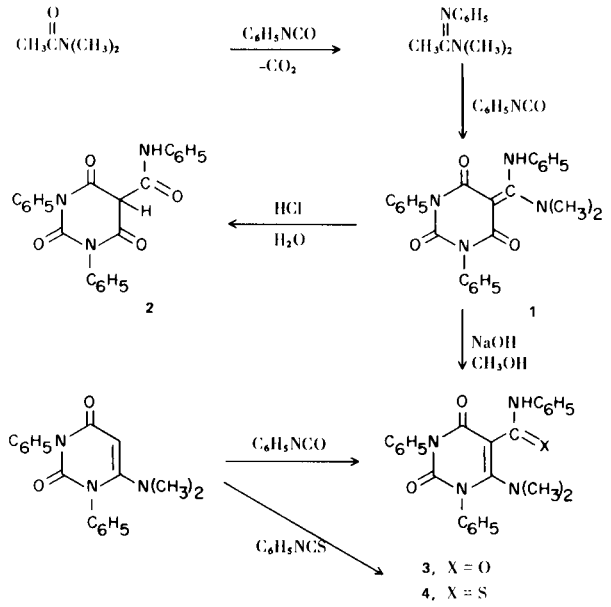
The products of the reactions of aryl isocyanates with *N,N*-disubstituted formamides or *N,N,N'*-trisubstituted formamidines include hexahydrotriazines and pentazaspirodecanetetraones, formed in good yields (3-6). However, when dimethylacetamide was heated with phenyl isocyanate, the complex reaction mixture gave, not the above heterocycles, but a substituted barbituric acid, **1** (Scheme I) in poor yields.

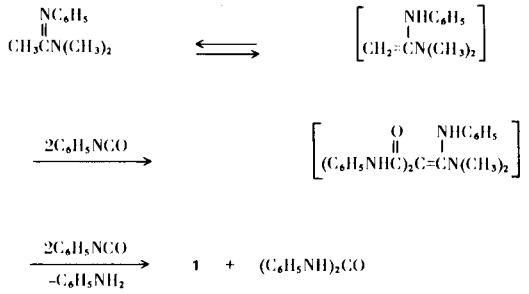
The structure of **1** was shown by its spectra and by acid hydrolysis to compound **2**, which was identical with a synthetic specimen. The mass spectrum of **1** included an intense peak of m/e 147 ($C_9H_{11}N_2^+$), which corresponded to the group $C_6H_5N{=}\overset{+}{C}\text{-}N(CH_3)_2$. The nmr spectrum showed, in addition to the requisite phenyl and methyl protons, a singlet at 10.5 δ, assigned to NH (7,8). The hydrolysis product **2**, best prepared by the action of phenyl isocyanate on 1,3-diphenylbarbituric acid, was previously obtained by Prelicz (9) through a different method.

SCHEME I



Compound **1** was also obtained from the reaction of phenyl isocyanate with *N,N*-dimethyl-*N'*-phenylacetamidine. This result may be explained by the well-known conversion of amides to amidines (10a,b). Subsequent reactions of this amidine to give **1** might involve a) a double carbamoylation at the methylene group of the enamine form, b) further reaction with phenyl isocyanate followed by ring closure and elimination of aniline as diphenyl urea (Scheme II).

SCHEME II

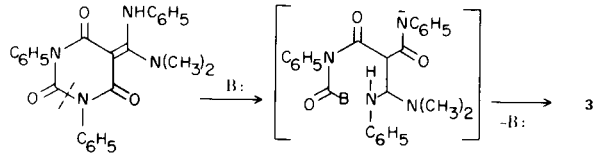


The replacement of the two methylene hydrogens of an enamine by phenyl isocyanate is analogous to a known reaction (11) of acetophenone-anil. It is of interest that the attempted reaction of phenyl isocyanate with an amidine unable to form an enamine, namely *N,N*-dimethyl-*N'*-phenylbenzamidine gave only recovered amidine and triphenyl isocyanurate.

Compound **1** was isomerized by methanolic sodium hydroxide to **3**, the structure of which was proved by independent synthesis. The known 6-chloro-1,3-diphenyluracil (12) was converted by dimethylamine to the new 6-dimethylamino-1,3-diphenyluracil, (**5**). This is analogous to the amination of 6-chloro-1,3-dimethyluracil (13). The reaction of **5** with phenyl isocyanate to give **3** is a typical enamine reaction, similar to the acetylation, at the 5-position, of 1,3-dimethyl-6-dimethylaminouracil (**14**). Another example of this reaction in the current work was the conversion of **5** to the thiocarboxanilide analog, **4**, by heating with phenyl isothiocyanate.

The mechanism of the alkaline isomerization of **1** to **3**

is not known. Attack by base at position 2 of the ring, followed by cleavage and recyclization, would give the desired product (15).



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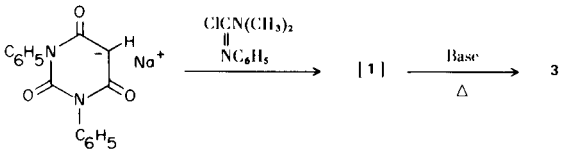
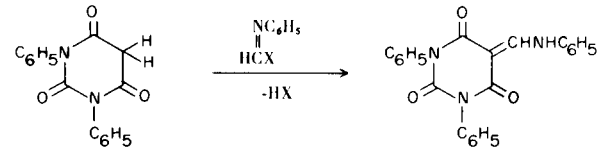
There are many examples of cleavage and reforming of pyrimidine rings in the Dimroth reaction (16), although cleavage rarely occurs at this location. However, cleavage between positions 2 and 3, similar to the 1,3-split proposed here, has been observed several times by Ueda and Fox (17).

An attempt to prepare compound **1** by treating the monosodium derivative of 1,3-diphenylbarbituric acid with *N,N*-dimethyl-*N'*-phenylchloroformamidine gave **3**. Heating a mixture of 1,3-diphenylbarbituric acid with the same reagent at 150° also yielded **3**, not **1**. One explanation of these results is to assume that compound **1** was formed initially and rearranged because of the basicity of residual sodium salt or unreacted amidine.



Further evidence of the tendency of 1,3-diphenylbarbituric acid to react with amidines at the 5-position is the formation of 5-anilinomethylene-1,3-diphenylbarbituric acid **6** with *N,N*-diphenylformamidine (18,19). In the current work, the same product **6** was obtained with either *N,N*-dimethyl-*N'*-phenylformamidine or ethyl *N*-phenylformimidate:

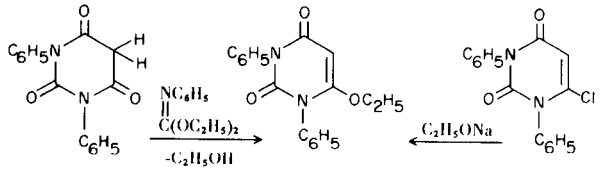


X = OC_2H_5, $N(CH_3)_2$

6

Although the above reactions occurred at the 5-position, the product **6** is different from compound **1** obtained by interaction of 1,3-diphenylbarbituric acid and *N,N*-dimethyl-*N'*-phenylchloroformamidine.

Treatment of 1,3-diphenylbarbituric acid with an imino ester, diethyl phenyliminocarbonate, brought about ethylation at the 6-position, giving 1,3-diphenyl-6-ethoxyuracil, **7**, which was identified by preparation from 6-chloro-1,3-diphenyluracil and sodium ethoxide:



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This reaction with sodium ethoxide is analogous to that done with 6-chloro-1,3-dimethyluracil (13).

EXPERIMENTAL

Melting points (corrected) were determined on a Fisher-Johns apparatus; ir spectra (in potassium bromide) on a Perkin-Elmer 337 or 137 spectrophotometer; nmr spectra on a Varian A-60A spectrometer, using deuteriomethyl chloride unless specified, and TMS as internal standard; mass spectra on a 21-110B-CEC double-focus mass spectrometer. All molecular weights were obtained from mass spectra.

5-[(Anilino, dimethylamino)methylene]-1,3-diphenylbarbituric Acid (**1**).

A mixture of 43.5 g. (0.50 mole) of dimethylacetamide and 59.5 g. (0.50 mole) of phenyl isocyanate protected from moisture was heated at 80-85° during stirring for 48 hours. On cooling, a precipitate of an unknown by-product separated, which was filtered, washed with methanol, and recrystallized from dimethylformamide; 2.0 g. of substance, m.p. 326-330° dec., was obtained; ir (potassium bromide) 1650-1660 cm^{-1} (C=O). Its formula corresponded to an $-NHC_6H_5$ derivative of 1,3-diphenyluracil, but attempts at synthesis from 4-chloro-1,3-diphenyluracil with aniline were unsuccessful.

Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82; O, 9.00; mol, wt., 355. Found: C, 74.34; H, 4.80; N, 11.64; O, 9.39; mol. wt., 355.

To the main syrupy filtrate was added 400 ml. of methanol and the mixture stirred for 3 hours. The resulting precipitate was filtered, washed, and stirred with 300 ml. of chloroform. The insoluble part consisted of 2.5 g. of 1,3-diphenylurea, m.p. 242-243° (undepressed on admixture with an authentic sample). The chloroform solution, after evaporation to dryness and recrystallization of the residue from ethanol gave 12.0 g. (18%, based on dimethylacetamide) of compound **1**, m.p. 253-255°; ir 1720-1725 (C=O), 1680-1685 cm^{-1} (C=O); nmr δ 2.6 (s, 6, $(CH_3)_2N$), 7.0-8.0 (m, 15, C_6H_5), and 10.5 (s, 1, NH); mass spectrum (70 eV) m/e 426, 334, 307, 215, 172, 147.

Anal. Calcd. for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14; mol. wt., 426. Found: C, 70.41; H, 5.21; N, 12.95; mol. wt., 426.

The methanol filtrate yielded, on standing, 1.0 g. of triphenyl isocyanurate, m.p. 278-280° (undepressed on admixture with an authentic sample), 30 g. of dimethylacetamide (by distillation), and 6.0 g. of 1,3-diphenylurea when the residue after distillation was stirred with methylene chloride. Removal of methylene chloride yielded a yellow oil which could not be crystallized by any

solvent. Chromatography on fluorosil with chloroform gave traces of triphenyl isocyanurate, 1,3-diphenylurea, and 1,1-dimethyl-3-phenylurea, but the bulk of the material, which should represent about 60% of the phenyl isocyanate used, remained an intractable oil.

When a mixture of 0.025 mole of *N*-phenyl-*N,N'*-dimethylacetamidine and 0.158 mole of phenyl isocyanate was heated for 6 days at 80-85° and the products separated as described above, a 10% yield of pure compound **1** was obtained, together with the same by-products.

Attempted Reaction of Phenyl Isocyanate with *N,N*-Dimethyl-*N'*-Phenylbenzamidine (20).

When a mixture of 0.02 mole of *N,N*-dimethyl-*N'*-phenylbenzamidine (21) and 0.02 mole of phenyl isocyanate was heated at 75° for 4 days, the products were 2.3 g. of triphenyl isocyanurate and 3.5 g. (77%) of the original *N,N*-dimethyl-*N'*-phenylbenzamidine.

1,3-Diphenyl-hexahydro-2,4,6-trioxo-5-pyrimidinecarboxanilide (**2**).

This compound, prepared by Prelicz (9) from the reaction of phenyl isothiocyanate on 1,3-diphenylbarbituric acid, followed by desulfurization with hydrogen peroxide, was obtained more conveniently by heating 1,3-diphenylbarbituric acid (0.01 mole) with phenyl isocyanate (0.25 mole) at 150° for 4 hours. The excess isocyanate was removed *in vacuo*, and the solid residue washed with ether. After recrystallization from ethanol and drying, a 63% yield of **2** was obtained as colorless needles, m.p. 226-228° (ref. (9), 202°); ir 1720-1725, 1660-1665 cm^{-1} (C=O); nmr δ 7.1-7.8 (m, 16, C_6H_5 and C*H*), and 12.1 (s, 1, N*H*).

Anal. Calcd. for $C_{23}H_{17}N_3O_4$: C, 69.16; H, 4.29; N, 10.52; mol. wt., 399. Found: C, 69.46; H, 4.18; N, 10.45; mol. wt., 399.

1,3-Diphenylhexahydro-2,4,6-trioxo-5-pyrimidine-*N*-*p*-tolylcarboxamide.

This compound, prepared in the same way as compound **2**, using *p*-tolyl isocyanate, melted at 247-248°, whereas Prelicz (9), after a two-step reaction, reported 202-204°. Our compound was pale yellow needles; ir 1720-1725, 1660-1665 cm^{-1} (C=O); nmr δ 2.3 (s, 3, CH_3), 7.0-7.9 (m, 16, C_6H_5 and C*H*), and 12.1 (s, 1, N*H*).

Anal. Calcd. for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16; mol. wt., 413. Found: C, 69.58; H, 4.46; N, 10.09; mol. wt., 413.

6-Dimethylamino-1,2,3,4-tetrahydro-2,4-dioxo-1,3-diphenyl-5-pyrimidinecarboxanilide (**3**).

A mixture of 2.0 g. (0.0067 mole) of 6-dimethylamino-1,3-diphenyluracil and 50 g. (0.42 mole) of phenyl isocyanate was heated at 140-150°. Within 10 minutes precipitation of **3** began. After 2 hours, the mixture was cooled, filtered, and the product washed with ether. Recrystallization from ethanol and drying (at 2 mm.) for 12 hours at 80° gave 2.2 g. (80%) of **3**, tiny colorless needles, m.p. 320-323° dec.; ir 3150 (NH), 1710-1715, 1630-1640 cm^{-1} (C=O).

Anal. Calcd. for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14; mol. wt., 426. Found: C, 70.50; H, 5.34; N, 13.14; mol. wt., 426.

Compound **3** was also obtained from compound **1** in 70% yield by refluxing a solution of 1.7 g. (0.004 mole) of **1**, 1.0 g. (0.025 mole) of sodium hydroxide and 50 ml. of methanol for 10 minutes. Cooling, neutralizing with 6*N* hydrochloric acid, diluting with 150 ml. of water, stirring, filtering, and washing with water, ethanol, and ether yielded the pure product.

Compound **3** was obtained in 52% yield by the reaction of 1,3 diphenyl-barbituric acid with *N,N*-dimethyl-*N'*-phenylchloroformamidine (22) at 150°, and in 33% yield by the reaction of the sodium salt of 1,3-diphenylbarbituric acid (formed with sodium hydride in dry tetrahydrofuran) with *N,N*-dimethyl-*N'*-phenylchloroformamidine.

6-Dimethylamino-1,2,3,4-tetrahydro-2,4-dioxo-1,3-diphenyl-5-pyrimidinethiocarboxanilide (**4**).

A mixture of 2.0 g. (0.0065 mole) of 6-dimethylamino-1,3-diphenyluracil (**5**) and 30 ml. (0.25 mole) of phenyl isothiocyanate was heated at 150° for 5 hours. The solid product, washed with ether and recrystallized from ethanol, consisted of 2.5 g. (90%) of **4**, m.p. 330-331° dec.

Anal. Calcd. for $C_{25}H_{22}N_4O_2S$: C, 67.85; H, 5.01; N, 12.66; mol. wt., 442. Found: C, 67.53; H, 4.91; N, 12.62; mol. wt., 442.

6-Dimethylamino-1,3-diphenyluracil (**5**).

A solution of 5.5 g. (0.018 mole) of 6-chloro-1,3-diphenyluracil (12), 75 ml. of dry methanol, and 10 g. (0.22 mole) of dimethylamine was refluxed for 30 minutes, the solvent removed, and the residue washed with ether, then water. The insoluble product, after recrystallization from a 1:1 ethanol-heptane mixture, consisted of 5.1 g. (93%) of **5**, as colorless needles, m.p. 204-205°; ir 1710-1715 and 1660-1665 cm^{-1} (C=O); nmr δ 2.5(s,6,$CH_3)_2N$), 5.3 (s,1,C-*H*), 7.0-7.8 (m,10,C_6H_5).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.57; N, 13.67. Found: C, 70.30; H, 5.80; N, 13.73.

5-Anilinomethylene-1,3-diphenylbarbituric Acid (**6**).

This compound was previously prepared by the reaction of 1,3-diphenylbarbituric acid with *N,N*-diphenylformamidine in refluxing ethanol (18) and with no solvent at 150° (19). In the current work a mixture of 1,3-diphenylbarbituric acid (2.0 g., 0.0071 mole) and ethyl *N*-phenylformimidate (23) (4.0 g., 0.027 mole) was heated at 150° for 10 minutes, to give **6**, m.p. 228-230° (93%) after recrystallization from ethanol. By a similar procedure, 0.0071 mole of 1,3-diphenylbarbituric acid reacted with 0.040 mole of *N,N*-dimethyl-*N'*-phenylformamidine (10b) in 2 hours at 150° to give an 81% yield of **6** after recrystallization. The structure of **6** proposed by Nightingale (18) was corroborated by nmr spectra and by analysis.

1,3-Diphenyl-6-ethoxyuracil (**7**).

A mixture of 0.23 g. of sodium (0.01 mole), dissolved in 30 ml. of absolute ethanol, and 3.0 g. (0.01 mole) of 6-chloro-1,3-diphenyluracil was refluxed for 30 minutes, the solvent evaporated, the residue stirred with water, and the product filtered. Recrystallization from methanol gave 2.2 g. (71%) of **7**, m.p. 186-187°; ir 1670-1675 and 1720-1725 cm^{-1} (C=O); nmr δ 1.05 (t, 3, CH_3), 3.9 (q, 2, CH_2), 5.25 (s, 1, C*H*), 7.0-7.7 (m, 10, C_6H_5).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.08; mol. wt.; 308. Found: C, 70.07; H, 5.31; N, 9.22; mol. wt., 308.

Compound **7** was also formed in 50% yield by the reaction of diethyl phenyliminocarbonate (24) with 1,3-diphenylbarbituric acid at 150°.

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