Synthesis and Some Reactions of Hexahydro-1,2,4-triazine-3,6-dione

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The synthesis of hexahydro-1,2,4-triazine-3,6-dione by hydrogenolysis of 1,2-dibenzylhexahydro-1,2,4-triazine-3,6-dione is reported. Ring contraction of the former dione to 3-amino-2,4-imidazolidinedione is discussed. The preparation of the 1- and 2-benzyl derivatives of hexahydro-1,2,4-triazine-3,6-dione and their conversion to the unsubstituted product are also described.

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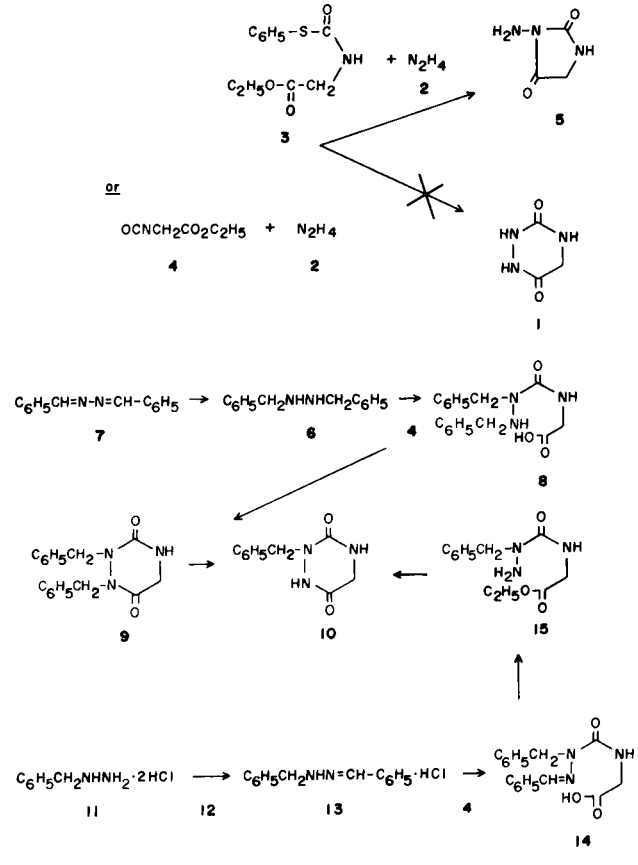
Hexahydro-1,2,4-triazine-3,6-dione (**1**) was initially prepared in 1952 by reaction of hydrazine (**2**) and mercapto compound (**3**) (1). Twelve years later Gante and Lautsch allegedly synthesized the same compound by reaction of ethyl isocyanatoacetate (**4**) and hydrazine (**2**) (2). Subsequently it was demonstrated that these investigators had actually isolated 3-amino-2,4-imidazolidinedione (**5**) instead of **1** (3,4). Since no other reports of triazine **1** have been forthcoming, it was of interest to prepare this compound.

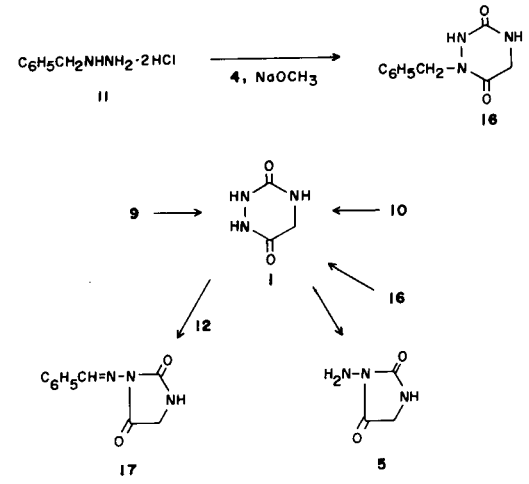
As a starting material for **1**, a 1,2-disubstituted hydrazine containing removable substituents was required. This compound would allow utilization of a variation of the Gante and Lautsch sequence in which cyclization to a five-membered ring is prohibited. This strategy would allow instead formation of a six-membered ring and result in preparation of a 1,2-disubstituted-1,2,4-triazine-3,6-dione. The final step of the proposed sequence would require removal of the substituents to form target compound **1**.



The desired starting material, 1,2-dibenzylhydrazine (**6**), was prepared by hydrogenation of benzalhydrazine (**7**). Reaction of **6** with isocyanate **4** followed by alkaline hydrolysis gave *N*-[(1,2-dibenzylhydrazino)carbonyl]glycine (**8**) which was cyclized to 1,2-dibenzylhexahydro-1,2,4-triazine-3,6-dione (**9**) with *p*-toluenesulfonic acid in refluxing toluene.

Hydrogenolysis of **9** using palladium-on-carbon in methanolic hydrogen chloride gave the 2-benzyltriazine-3,6-dione **10** instead of the desired product **1**. To prove the structure of the monobenzyl compound **10** the product was synthesized unequivocally in a four-step sequence originating with benzylhydrazine dihydrochloride (**11**).

Reaction of **11** with benzaldehyde (**12**) gave the Schiff base **13** which upon treatment with **4** and subsequent hydrolysis afforded *N*-[(2-benzylidene-1-benzylhydrazino)-carbonyl]glycine (**14**). Boiling of **14** with aqueous acid followed by treatment with ethyl alcohol and sulfuric acid gave rise to the ester **15** which was cyclized to **10** in alcoholic base. The product obtained from this route and the monobenzyl product obtained by hydrogenolysis of **9** were



identical in all respects. As a corollary to this work, 1-benzylhexahydro-1,2,4-triazine-3,6-dione (**16**) was prepared by reaction of benzylhydrazine hydrochloride (**11**) with **3** in alcoholic base.

Hydrogenolysis of **9** using palladium-on-carbon in ethyl acetate in the presence of a catalytic amount of ethanolic hydrogen chloride gave the desired hexahydro-1,2,4-triazine-3,6-dione **1** which was also obtained by similar catalytic hydrogenolysis of the monobenzyl compounds **10** and **16**.

Treatment of **1** with benzaldehyde (**12**) in acetic acid gave the ring-contracted benzylideneamino compound **17** (5) while **1** in refluxing methanolic hydrogen chloride and subsequent treatment with base gave rise to 3-amino-2,4-imidazolidinedione **5**. The formation of **5** under these conditions raises the possibility that Gante and Lautsch (2) formed **1** *in situ* upon the reaction of **2** and **4** but subsequent conversion of **1** to **5** occurred under the reaction conditions.

EXPERIMENTAL

Melting points were taken in a Mel-Temp apparatus in open capillary tubes and are uncorrected. The nuclear magnetic resonance spectra were taken on a Varian A-60A instrument and were compared with TMS as an internal standard. Infrared spectra were determined as Nujol Mulls on a Perkin-Elmer 137B spectrophotometer. The mass spectra were run on a Finnegan 3300 mass spectrometer at Cornell University, Ithaca, New York.

1,2-Dibenzylhydrazine (**6**).

A mixture of 41.6 g (0.20 mole) of **7**, 1.0 g 5% of Pd/C (50% moisture), and 500 ml of methanol was shaken with hydrogen on a Parr apparatus for 30 minutes whereupon the theoretical quantity of hydrogen was consumed. The catalyst was filtered and washed with 2 × 75 ml of methanol. The filtrate and combined washings were used directly in the next step.

N-[(1,2-Dibenzylhydrazino)carbonyl]glycine (**8**).

To the above solution heated at 40° was added over 15 minutes 25.8 g (0.20 mole) of **4**, the temperature rising to 48° during the addition. After the solution was stirred and refluxed for 1 hour, sodium methoxide (10.8 g, 0.20 mole) was added; refluxing was continued for an additional 1.25 hours. Water (100 ml) was added and, after a 45 minute reflux period, the mixture was concentrated to dryness *in vacuo*. The residue was suspended in 300 ml of water. The mixture was made acidic with concentrated hydrochloric acid and extracted with 2 × 275 ml of chloroform. The extracts were dried (magnesium sulfate) and concentrated to dryness *in vacuo* to give 61 g of the crude product. Recrystallization from 500 ml of toluene gave 56.3 g (89%) of **8**, mp 127-131°. Further recrystallization from toluene gave an analytical sample, mp 125-127°; nmr (DMSO-d_6): δ 3.68-3.83 (m, 4, ArCH_2NH and NHCH_2CO$_2$H), 4.65 (s, 2, ArCH_2N=), 7.32 (s, 10, aromatic C-H); ir: (μ) 3.00, 3.09 (NH), 3.60-4.30 (NH and CO_2H), 5.80-6.15 (C=O).

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 64.88; H, 6.08; N, 13.27.

1,2-Dibenzylhexahydro-1,2,4-triazine-3,6-dione (**9**).

A mixture of 31.20 g (0.10 mole) of **8**, 5.0 g of *p*-toluenesulfonic acid monohydrate and 500 ml of toluene was stirred and refluxed for five hours using a Dean-Stark apparatus. An additional 5.0 g of the sulfonic acid was added and refluxing was continued for another three hours. Total amount water evolved: 2.65 ml; theoretical (including the amount from the sulfonic acid): 2.80 ml.

The mixture was concentrated to dryness *in vacuo*, the residue was suspended in 500 ml of water and the mixture was made alkaline with potassium carbonate in water. The mixture was extracted with 2 × 350 ml of chloroform and the combined extracts were washed with 300 ml of water, dried (magnesium sulfate) and concentrated to dryness *in vacuo* to give 26 g of the crude product. Recrystallization from 125 ml of toluene gave, in two crops, 18.8 g (64%) of the product, mp 113-116°; nmr (DMSO-d_6): δ 3.40-3.47 (m, collapses to s in deuterium oxide, 3, N*H*, and -CH_2NH), 4.65 and 4.80 (2s, 4, ArCH_2), 7.37 (s, 10, aromatic C-H); ir: (μ) 3.11 (N-H), 5.94 (C=O).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 69.09; H, 5.74; N, 14.13.

2-Benzylhexahydro-1,2,4-triazine-3,6-dione (**10**) from **9**.

A mixture containing 1.47 g (0.005 mole) of **9**, 1.0 g of 5% Pd/C (50% moisture), 140 ml of methanol and 10 ml of ethanolic hydrogen chloride was shaken with hydrogen on a Parr apparatus for 12 minutes, hydrogen uptake: 8.0#; theoretical amount: 5.0#. Longer hydrogenation periods failed to result in the consumption of additional quantities of hydrogen. The catalyst was filtered and washed with 4 × 150 ml of methanol. The filtrate and combined washings were concentrated to dryness *in vacuo*. Recrystallization from methanol gave in two crops of 0.52 g (50%) of **10**, the infrared spectrum of which was identical with a sample of the product obtained from **15**.

The catalyst above was boiled with water. No appreciable solid was isolated upon evaporation of the aqueous extract solution, indicating that **1** was not formed in the hydrogenation.

N-Benzylidenebenzylamine Hydrochloride (**13**).

To a solution of 58.5 g (0.30 mole) of **11** in 500 ml of methanol stirred at 20-30° was added quickly 46.6 g (0.44 mole) of benzaldehyde (**12**). The solution was stirred and refluxed for 1 hour and concentrated to dryness *in vacuo*. Recrystallization from ethyl acetate gave 65 g (88%) of **13**. Further recrystallization from ethyl acetate gave an analytical sample, mp 142-144°; ir: (μ) 2.65-4.25 (⁺NH), 6.10 (CN).

Anal. Calcd. for $C_{14}H_{14}N_2$·HCl: C, 68.14; H, 6.12; N, 11.35. Found: C, 68.19; H, 6.07; N, 11.40.

N-[(2-Benzylidene-1-benzylhydrazino)carbonyl]glycine (**14**).

To a suspension of 38.3 g (0.156 mole) of **13** in 500 ml of absolute ethanol was added quickly 15.7 g (0.156 mole) of triethylamine followed by 20.1 g (0.156 mole) of **4**. The mixture was stirred and refluxed for three days and concentrated to dryness *in vacuo*. The residue was suspended in 400 ml of water and the product was extracted with 2 × 200 ml of chloroform. After the chloroform solution was dried and concentrated to dryness *in vacuo*, the residue, 400 ml of 10% potassium hydroxide, and 100 ml of methanol was stirred and refluxed for 2 hours, cooled, and acidified with concentrated hydrochloric acid. The mixture was extracted with 450 ml of chloroform and the product was recrystallized from 100 ml of acetonitrile to give 30.6 g (67%) of **14**. Further recrystallization from acetonitrile gave an analytical sample, mp 146-149°; nmr (DMSO-d_6): δ 3.82 (m, 3, N*H* and CH_2NH), 5.27 (s, 2, ArCH_2N=), 7.37-7.73 (m, 11, aromatic C-H and =C-H); ir: (μ) 2.93 (N-H), 5.70, 6.07 (C=O), 6.19 (C=C).

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.50; H, 5.34; N, 13.34.

Ethyl *N*-[(1-Benzylhydrazino)carbonyl]glycinate (**15**).

A mixture of 81 g (0.26 mole) of **14**, 700 ml of water and 500 ml of concentrated hydrochloric acid was stirred and refluxed for 4 hours. The volatile products were distilled and water was added periodically to maintain volume. The solution was concentrated to dryness *in vacuo*, the residue was dissolved in 300 ml of absolute ethanol and 20 ml of concentrated sulfuric acid was added. After a 6 hour reflux period the solution was diluted with 500 ml of water, made alkaline with potassium carbonate and extracted with 3 × 150 ml of chloroform. The chloroform extracts were dried (magnesium sulfate) and concentrated to dryness *in*

vacuo. Recrystallization from toluene gave 13.1 g (20%) of **15**. Further recrystallization from toluene gave an analytical sample, mp 112-114°; nmr (DMSO-d_6): δ 1.20 (t, 3, CH_3CH_2O), 3.47 (broad s, 2, exchangeable, NH_2), 3.75-3.81 (m, 4, $NHCH_2CO$ and $ArCH_2N$=), 4.10 (q, 2, CH_3CH_2O-), 7.44 (s, 5, aromatic C-H); ir: (μ) 2.99, 3.03 (N-H), 5.70, 6.05 (C=O), 8.20-8.30 (C-O-C).

Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.35; H, 6.82; N, 16.72. Found: C, 57.02; H, 6.74; N, 16.80.

2-Benzylhexahydro-1,2,4-triazine-3,6-dione (**10**) from **15**.

A solution of 1.26 g (0.005 mole) of **15**, 0.54 g (0.01 mole) of sodium methoxide and 100 ml of methanol was stirred and refluxed for 18 hours. After the mixture was concentrated to dryness *in vacuo*, the residue was dissolved in 40 ml of water and the solution was made acidic with dilute hydrochloric acid. Extraction with chloroform, concentration to dryness and recrystallization from acetonitrile gave 0.10 g (10%) of **10**, the infrared spectrum of which was identical with that of the product derived from **9**. An analytical sample of **10**, mp 198-200°, was obtained by recrystallization from methanol; nmr (DMSO-d_6): δ 3.41 (s, 2, exchangeable, NH), 3.75 (s, 2, $NHCH_2$), 4.68 (s, 2, $ArCH_2N$), 7.32 (s, 5, aromatic C-H); ir: (μ) 3.05, 3.17 (N-H), 5.80, 5.91, 6.03 (C=O); ms: M^+ m/e 205.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.52; H, 5.32; N, 20.39.

1-Benzylhexahydro-1,2,4-triazine-3,6-dione (**16**).

To a solution of 39.0 g (0.20 mole) of benzylhydrazine dihydrochloride (**11**) in 500 ml of methanol stirred at 10° was added quickly 21.6 g (0.40 mole) of sodium methoxide whereupon the temperature rose to 30°. The mixture was cooled at 10-17° and 25.8 g (0.20 mole) of **4** was added over 5 minutes. After a 2.5 hour reflux period another 10.8 g (0.20 mole) of sodium methoxide was added. The mixture was stirred and refluxed for 4 hours, concentrated to dryness *in vacuo*, and the residue was dissolved in 400 ml of water. The solution was acidified with dilute hydrochloric acid and, after storage overnight in the refrigerator, the solid was filtered and dried to give 25.2 g (62%) of **16**. Recrystallization from methanol gave an analytical sample, mp 206-208°; nmr (DMSO-d_6): δ 3.68 (s, 2, $NHCH_2$), 4.65 (s, 2, $ArCH_2N$), 7.55 (s, 5, aromatic C-H); ir: (μ) 3.17 (N-H), 6.00 (C=O); ms: M^+ m/e 205.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.74; H, 5.51; N, 20.54.

The infrared and nuclear magnetic resonance spectra of the product **16** were not the same as those of the monobenzyl product **10** obtained from **15**.

Hexahydro-1,2,4-triazine-3,6-dione (**1**).

A mixture containing 17.70 g (0.06 mole) of **9**, 10.0 g of 5% Pd/C (dry), 6.0 ml ethanolic hydrogen chloride and 450 ml of ethyl acetate was shaken with hydrogen at 3-4 atmospheres for two weeks on a Parr apparatus; hydrogen uptake: 11.1 #, theoretical: 8.0 #. To the mixture was added *ca.* 20 g of charcoal. The mixture was filtered and the catalyst-charcoal material was washed with 3 × 75 ml of methanol. The filtrate and washings were discarded and the catalyst mixture was extracted with 500 ml of boiling water for 30 minutes followed by 400 ml of boiling dimethylformamide for 10 minutes. The combined extracts were concentrated to dryness *in vacuo* to give a white solid which was triturated with 60 ml of methanol. After the mixture was refrigerated for 30 minutes, the solid was filtered, washed with 3 × 15 ml of methanol, air dried and dried at 60° to give 4.90 g (71%) of the product, mp 222-226°. An analytical sample, mp 227-228°, was obtained by recrystallization from water; nmr (TFA) δ: 4.08 (s, 2, $NHCH_2CO$); ir: (μ) 3.10-3.30 (N-H), 5.81-6.10 (CO); ms: M^+, m/e 115.

Anal. Calcd. for $C_3H_5N_3O_2$: C, 31.31; H, 4.38; N, 36.51. Found: C, 31.27; H, 4.37; N, 36.37.

The infrared spectrum of **1** was not similar to that of an authentic sample of 3-amino-2,4-imidazolidinedione (**5**) (6); ir: (μ) 3.10 (N-H), 5.60, 5.80-5.85 (C=O).

Hexahydro-1,2,4-triazine-3,6-dione (**1**) from **10**.

A mixture of 2.05 g (0.01 mole) of **10**, 150 ml of ethyl acetate, 2.0 g 5% of Pd/C (dry) and 2.0 ml ethanolic hydrogen chloride was shaken with hydrogen at 3-4 atmospheres for five days on a Parr apparatus; hydrogen uptake: 12.3 #; theoretical 10.0 #. The mixture was diluted with 10 g of charcoal and filtered. The charcoal mixture was washed with 3 × 25 ml methanol and boiled with 200 ml of water for 20 minutes. The aqueous extract solution was concentrated to dryness *in vacuo* and the residue was stirred with 10 ml of methanol. Filtration gave 0.49 g (43%) of **1**, the infrared spectrum of which was identical with the product obtained from **9**.

Hexahydro-1,2,4-triazine-3,6-dione (**1**) from **16**.

Hydrogenation of a 2.05 g (0.01 mole) of sample of **16** for 24 hours using the same quantities of reagent and work-up as described for **10** gave 0.41 g (36%) of **1**, the infrared spectrum of which was identical to the product obtained from **9**.

3-(Benzylideneamino)-2,4 -imidazolidinedione (**17**) from **1**.

A mixture of 0.16 g (0.0014 mole) of **1**, 12 ml of glacial acetic acid, and 0.16 g (0.0015 mole) of benzaldehyde (**12**) was stirred and refluxed for 20 hours and concentrated to dryness *in vacuo*. The residue was dissolved in 6 ml of ethyl acetate and, after cooling, 0.03 g of an unidentified product was collected. The ethyl acetate filtrate was concentrated to dryness and the residue was slurried with 3 ml of methanol to give 0.05 g (17%) of the product, the infrared spectrum of which was identical to that of an authentic sample of **17** prepared from **5** and **12**.

3-(Benzylideneamino)-2,4-imidazolidenedione (**17**) from **5** and **12**.

A mixture of 1.15 g (0.01 mole) of **5**, 1.06 g (0.01 mole) of **12**, two drops concentrated hydrochloric acid and 50 ml of methanol was stirred and refluxed for 2 hours and cooled. Filtration gave 0.93 g (45%) of the product, mp 195-197°; ir: (μ) 3.05 (N-H), 5.60, 5.77, 5.83 (C=O).

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68. Found: C, 58.97; H, 4.44; N, 20.49.

3-Amino-2,4-imidazolidinedione (**5**) from **1**.

A mixture of 0.50 g (0.0044 mole) of **1**, 5 ml of concentrated hydrochloric acid and 50 ml of methanol was stirred and refluxed for 45 minutes and then concentrated to dryness *in vacuo*. The residue was dissolved in 30 ml of methanol and, after 0.40 g sodium methoxide was added, the mixture was stirred and refluxed for 20 minutes. Ethanolic hydrogen chloride was added to *p*H 7 and the mixture was concentrated to dryness *in vacuo*. Recrystallization from 10 ml of ethanol-water (3:1) gave, in two crops, 0.14 g (28%) of **5**, the infrared spectrum which was identical with an authentic sample prepared by the literature method (6).

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