1,2,4-Triazino[4,3-*c*]- and [2,3-*c*]quinazolines

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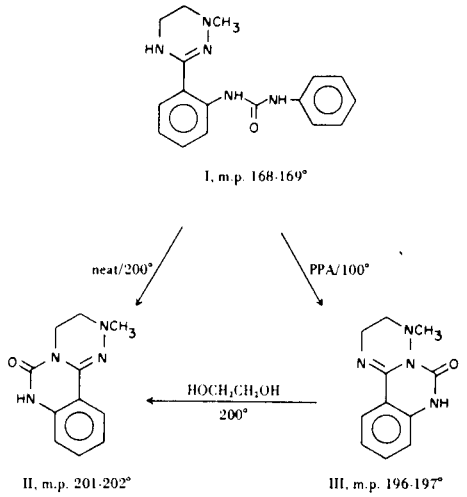
This paper describes the reactions of 2-*o*-aminophenyl-1,4,5,6-tetrahydro-1-methyl-1,2,4-triazine with a variety of reagents to give substituted 1,2,4-triazino[4,3-*c*]quinazolines or 1,2,4-triazino[2,3-*c*]quinazolines. Certain representative compounds of these two new heterocyclic systems were characterized by the tlc, ir, nmr, mass spectra, and identified by unequivacol synthesis.

We have found that heating 1-(*o*-(1,4,5,6-tetrahydro-1-methyl-1,2,4-triazin-3-yl)phenyl)-3-phenylurea (I) at 200° for 0.5 hour caused the loss of aninline and formation of 2,3,4,7-tetrahydro-2-methyl-6*H*-1,2,4-triazino[4,3-*c*]quinazolin-6-one (II), and heating I with PPA at 100° for 3 hours caused the loss of aniline and formation of 2,3,4,7-tetrahydro-4-methyl-6*H*-1,2,4-triazino[2,3-*c*]quinazolin-6-one (III).

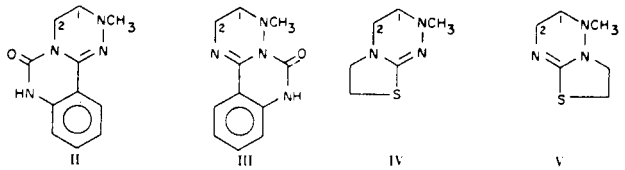


Triazinoquinazolinones II and III are new heterocyclic systems. They were characterized by tlc, ir, pmr, and mass spectra, and identified by unequivocal synthesis.

Good tlc separation was obtained when the compounds were spotted from a methanol solution on silicic acid and developed by 1:10 methanol:chloroform (Rf's II = 0.42 and III = 0.62). This eliminated the possibility of II and III being two different crystalline forms of the same compound. The tlc spot of III developed a yellow color upon standing while II showed no discoloration.

Ir spectra (nujol) of II and III were vastly different within the fingerprint region, and the C=O absorption of II and III was 1695 and 1730 cm^{-1}, respectively. The 35 cm^{-1} higher frequency for the C=O of III is analagous to a C=O absorption of 1690 cm^{-1} for *N*-phenylsemicarbazide as compared to 1660 cm^{-1} for *N*-phenylurea. The higher C=O frequency for III and *N*-phenylsemicarbazide is due to the electron withdrawing effect of the additional nitrogen (N-CO-N *vs* N-CO-N-N).

A comparison of the pmr spectra of II and III with 3,4,6,7-tetrahydro-2-methyl-2*H*-thiazolo[2,3-*c*][1,2,4]triazine (IV) and 2,3,6,7-tetrahydro-5-methyl-5*H*-thiazolo-[3,2-*b*][1,2,4]triazine (V) indicated comparable differences in resonance for the $-CH_2CH_2-$ and NCH_3 protons of the triazine ring (1). In all four compounds the $-CH_2CH_2-$ exhibits a typical A_2B_2 spectrum with J = 5.0 Hz.



	II	III	IV	V
δ NCH_3	2.72	2.57	2.72	2.56
CH_2 (1)	2.85	3.00	2.75	2.80
CH_2 (2)	3.82	3.53	3.57	3.50

The mass spectra of II and III were obtained by direct probe at 80 eV and were scanned at ~ 130°. As expected the fragmentation patterns were quite similar. However, II has the molecular ion as the base peak whereas for III the base peak is 174, which is the molecular ion minus 42. This most likely is a loss of $CH_2CH_2N\cdot$ as follows:

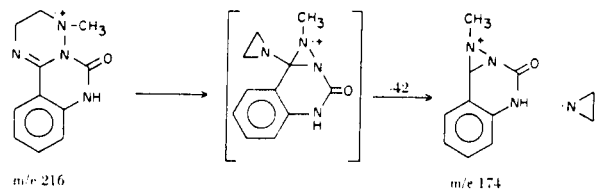
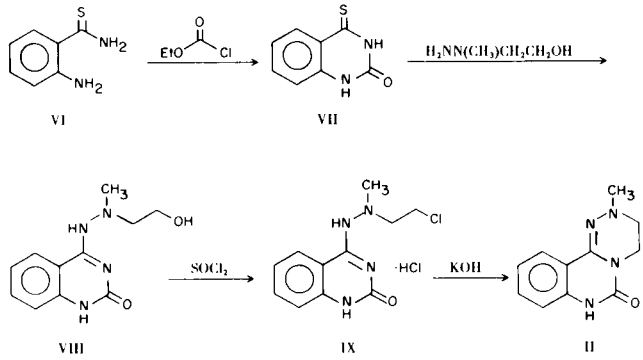


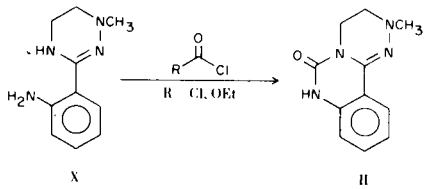
Table I

m/e	216	201	188	187	186	174	173	172	171	147	146	145	144
II	500	50	20	40	70	30	20	25	20	25	20	100	50
III	140	10	75	15	20	200	40	165	20	5	25	100	45

Triazinoquinazolinone II was synthesized by an unequivocal method. *o*-Aminothiobenzamide VI was allowed to react with ethyl chloroformate in refluxing pyridine to afford 2-oxo-4-thiono-1,2,3,4-tetrahydroquinazoline (VII), which on treatment with 1-methyl-1-(β-hydroxyethyl)-hydrazine gave 1,2-dihydro-4-(2-β-hydroxyethyl-2-methyl-hydrazino)quinazolin-2-one (VIII). Treatment of VIII with thionyl chloride afforded 1,2-dihydro-4-(2-β-chloroethyl-2-methylhydrazino)quinazolin-2-one hydrochloride (IX). Base catalyzed (potassium hydroxide) cyclodehydrochlorination of IX gave triazinoquinazolinone II.

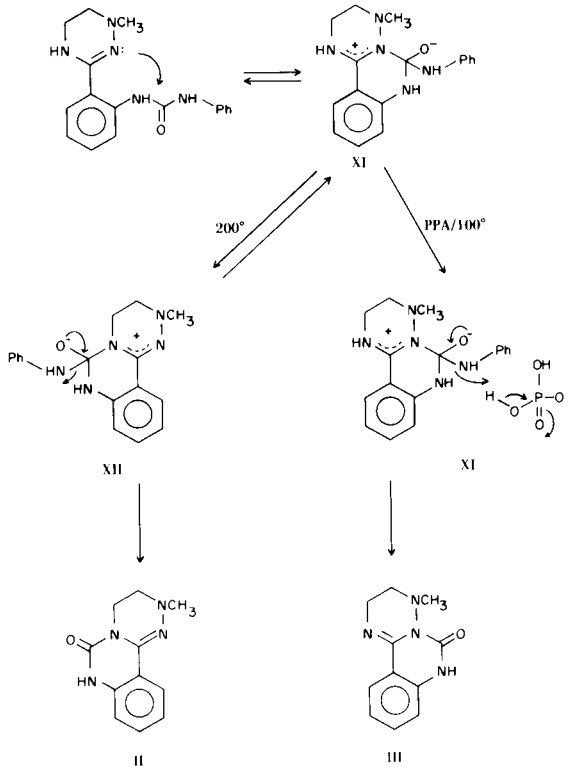


Triazinoquinazolinone II is the thermodynamically stable isomer as evidenced by the fact that heating triazinoquinazolinone III at 200° in ethylene glycol isomerized it to II. Also, when 3-(*o*-aminophenyl)-1,4,5,6-tetrahydro-1-methyl-1,2,4-triazine (X) was allowed to react with ethyl chloroformate and with phosgene, in both cases, triazinoquinazolinone II was formed. In neither case was the formation of any III observed.

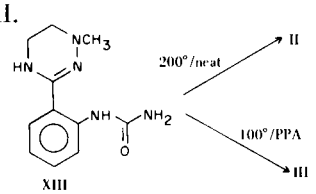


The formation of the less stable isomer III in PPA may occur because the PPA facilitates the loss of aniline from intermediate XI by supplying a proton, whereas in the absence of PPA (neat at 200°) intermediate XI is in equilibrium with XII, and XII is the less energetic intermediate which then goes to product II.

We were interested in the effect the phenyl group in urea I may exert on the course of the ring closure reactions



affording II and III. Therefore we synthesized 1-(*o*-(1,4,5,6-tetrahydro-1-methyl-1,2,4-triazin-3-yl)phenyl)urea (XIII), which has a proton in place of the phenyl at N^3. The two most obvious differences between I and XIII are more steric crowding in the case of I especially when ring closure occures at N^2 due to interaction of phenyl with the CH_3 at N^1, and a difference in the basicity of the two leaving groups aniline (pK_b 9.38) and NH_3 (pK_b 4.75). The reduction of steric hindrance with XIII might result in preference for formation of III instead of II. Changing the leaving group from aniline to the more basic NH_3 should increase the energy of the intermediate or transition state going from XIII to either II or III, especially in the case of II which is done neat in the absence of any acid. Albeit urea XIII behaved the same as urea I. When it was heated neat at 200° it afforded II, and when it was heated at 100° in PPA it gave III.



EXPERIMENTAL

The melting points were obtained in a capillary tube with the Thomas-Hoover Uni-Melt and are uncorrected. The elemental analyses were done by Midwest Microlabs, Inc., Indianaplis, Indiana. The pmr spectra were obtained with a Varian A-60 using TMS as an internal standard. Infrared spectra were obtained with a Perkin-Elmer 337 grating spectrophotometer. Mass spectra were obtained with a CEC-490.

1-(*o*-(1,4,5,6-Tetrahydro-1-methyl-1,2,4-triazin-3-yl)phenyl-3-phenylurea (I).

A mixture of 5.7 g. (0.03 mole) 3-(*o*-aminophenyl)-1,4,5,6-tetrahydro-1-methyl-1,2,4-triazine (X), 3.6 g. (0.03 mole) phenyl isocyanate, and 75 ml. of ethanol was heated at reflux overnight, concentrated *in vacuo*, cooled, and suction filtered to give 7.2 g. (77%) of white crystalline solid, m.p. 165-167°. Analytical sample (2-propanol) m.p. 168-169°; ir (nujol): 3350, 3310, 3230, 3160 (NH), 1675 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{19}N_5O$: C, 65.89; H, 6.19; N, 22.64. Found: C, 65.63; H, 6.25; N, 22.26.

2,3,4,7-Tetrahydro-2-methyl-6*H*-1,2,4-triazino[4,3-c]quinazolin-6-one (II).

A 3.0 g. (0.01 mole) sample of urea I was kept at 200° for 0.5 hour, allowed to cool, and the solid triturated with ethanol to give 2.0 g. (100%) of white solid, m.p. 198-200°. Analytical sample (2-ptopanol) melted at 201-202°.

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 61.09; H, 5.59; N, 25.91. Found: C, 61.29; H, 5.43; N, 26.04.

2,3,4,7-Tetrahydro-4-methyl-6*H*-1,2,4-triazino[2,3-c]quinazolin-6-one (III).

A mixture of 4.0 g. (0.013 mole) urea I and 35 g. of PPA was stirred and heated on a steam-bath for 3 hours, treated with 150 g. of crushed ice, basified with sodium carbonate solution, and extracted with chloroform. The washed (water) and dried magnesium sulfate) chloroform extract was evaporated *in vacuo* to give 2.7 g. of white solid which was recrystallized from ethanol to afford 1.8 (69%) of white crystals, m.p. 195-197°. Analytical sample (ethanol) melted at 196-197°.

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 61.09; H, 5.59; N, 25.91. Found: C, 61.21; H, 5.60; N, 26.06.

o-Aminothiobenzamide (VI).

A mixture of 100 g. (0.85 mole) of anthranilonitrile, 500 ml. of pyridine, and 100 ml. triethylamine was treated with gaseous hydrogen sulfide for a 3 hour period, stirred for 18 hours, and evaporated to dryness *in vacuo*. The solid residue was washed with ethanol-water, and recrystallized from water to give 92 g. (78%) of yellow solid, m.p. 121-122°.

2-Oxo-4-thiono-1,2,3,4-tetrahydroquinazoline (VII).

A mixture of 30.4 g. (0.2 mole) of *o*-aminothiobenzamide, 21.6 g. (0.2 mole) ethyl chloroformate, and 150 ml. of pyridine was heated at reflux for 3 hours, cooled, diluted with 1000 ml. of water, neutralized with hydrochloric acid, and the yellow precipitate suction filtered. The yellow solid was suspended in 100 ml. water treated with 1*N* potassium hydroxide until dissolved, 20 ml. of 3*N* potassium hydroxide added, allowed to stand overnight, acidified with hydrochloric acid, and the solid suciton filtered, m.p. 270-272°, yield 26.7 (81%).

4-(2-(β-Hydroxyethyl)-2-methylhydrazino)-2(1*H*)quinazolinone (VIII).

A mixture of 16.6 g. (0.1 mole) of 2-oxo-4-thiono-1,2,3,4-tetrahydroquinazoline (VII), 11.7 g. (0.13 mole) of 1-(β-hydroxyethyl)-1-methylhydrazine, and 50 ml. of DMF was stirred at ambient temperature for 4 days. The precipitate was suction filtered and washed with cold 2-propanol to give 17 g. (74%) of off-white solid, m.p. 153-157°. Two recrystallizations from 2-propanol afforded 12.5 g. (54%) of white crystalline solid, m.p. 161-162°; pmr (D_6MSO): δ 2.78 (s, 3H, NCH_3), 3.05 (m, 2H, CH_2), 3.79 (m. 2H, CH_2), 7.1-8.2 (m, 4 aromatic H).

Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.27; H, 5.84; N, 24.25.

4-(2-(β-Chloroethyl)-2-methylhydrazino)-2(1*H*)quinazolinone Hydrochloride (IX).

4-(2-(β-Hydroxyethyl)-2-methylhydrazino)-2(1*H*)quinazoline (VII) (4.0 g.) was added, portionwise, to 50 ml. of cooled (5°), sitrred thionyl chloride. The mixture was stirred and heated at 50-60° for 2 hours. The thionyl chloride was evaporated *in vacuo* and the residue was washed with dry ether to give 4.4 g. of tan gummy solid. This material resisted purification so it was used as is for base-catalyzed cyclization to triazinoquinazolinone II.

2,3,4,7-Tetrahydro-2-methyl-6*H*-1,2,4-triazino[4,3-c]quinazolin-6-one (II).

The tan gummy solid (4-(2-(β-chloroethyl)-2-methylhydrazino)-2(1*H*)quinazolinone) was dissolved in methanol, a solution of 1.0 g. of sodium methoxide in 50 ml. of methanol was added, and the mixture was heated on the steam bath for 1 hour. The methanol was evaporated *in vacuo*. The residue was treated with dilute sodium hydroxide solution and extracted with chloroform. The washed (water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo* to give 1.1 g. of white solid m.p. 198-200°, recrystallization from ethanol, m.p. 201-202°.

3-(*o*-Aminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (X).

A stirred mixture of 61 g. (0.4 mole) of anthranilthioamide, 40 g. (0.45 mole) of *N*-(β-aminoethyl)-*N*-methylhydrazine, and 100 ml. of 2-propanol, through which dry nitrogen was bubbled. was heated with an oil-bath at 145-155° for 30 minutes. The mixture was cooled and the solid recrystallized twice from 2-propanol, m.p. 139-141°, yield 37 g. (48%).

Anal. Calcd. for $C_{10}H_{14}N_4$: C, 63.13; H, 7.41; N, 29.45. Found: C, 63.37; H, 7.24; N, 29.45.

Triazinoquinazolinone II from 3-(*o*-Aminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine X and Ethyl Chloroformate.

A stirred mixture of 5.7 g. (0.03 mole) of X, 3.2 g. (0.03 mole) of ethyl chloroformate, and 5 ml. of triethylamine was stirred and heated on a steam-bath for 2 hours. The cooled mixture was treated with chloroform and washed with water. The dried (magnesium sulfate) chloroform solution was evaporated *in vacuo* and the residue recrystallized twice from ethanol to give 4.0 g. (66%) white solid II, m.p. 198-199°.

Triazinoquinazolinone II from 3-(*o*-Aminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine X and Phosgene.

To a stirred, cooled mixture of 5.7 g. (0.03 mole) of X, 5 ml. of triethylamine, and 150 ml. of methylene chloride was added phosgene gas at a moderate rate for a 5 minute period. The mixture was stirred at ambient temperature overnight, diluted with 200 ml. of methylene chloride, and washed three times with 100-ml. portions of water. The dried (magnesium sulfate) chloroform sulution was evaporated *in vacuo* and the residue recrystallized twice from ethanol, m.p. 198-200°, yield 3.2 g. (53%).

1-(*o*-(1-Methyl-1,4,5,6-tetrahydro-1,2,4-triazin-3-yl)phenyl)urea (XII).

To a stirred, warmed mixture of 9.5 g. (0.05 mole) of X, 3 ml. of glacial acetic acid, and 200 ml. of water was added, dropwise, over a 20 minute period, a solution of 4.3 g. of potassium cyanate in 100 ml. of water. The solution was stirred for 2 hours, concentrated *in vacuo*, and the crystalline material which precipitated was suction filtered, washed with water, and recrystallized twice from ethanol, m.p. 181-182°, yield 9.2 g. (78%).

Anal. Calcd. for $C_{11}H_{15}N_5O$: C, 56.63; H, 6.48; N, 30.2. Found: C, 56.89; H, 6.35; N, 30.39.

Triazinoquinazolinone II from Thermal Cyclization of Triazinophenylurea XII.

Triazinophenylurea XII (5.0 g.) was heated with an oil bath at 220° for 1 hour. The cooled residue was recrystallized twice from ethanol with charcoal to give 2.8 g. of triazinoquinazolinone II, m.p. 199-201°.

Triazinoquinazolinone III from PPA Cyclization of Triazinophenylurea XII.

Triazinophenylurea XII (5.0 g.) and 50 g. of polyphosphoric acid was stirred and heated at 100° for 3 hours, treated with crushed ice, basified with sodium carbonate, and extracted with chloroform. The dried (sodium sulfate) chloroform solution was evaporated and the residue recrystallized twice from ethanol to give 2.8 g. of triazinoquinazolinone III, m.p. 195-197°.

REFERENCES

(1) D. L. Trepanier and P. E. Krieger *J. Heterocyclic Chem.*, 7, 1231 (1970).