A One-step Synthesis of the *as*-Triazine Ring System

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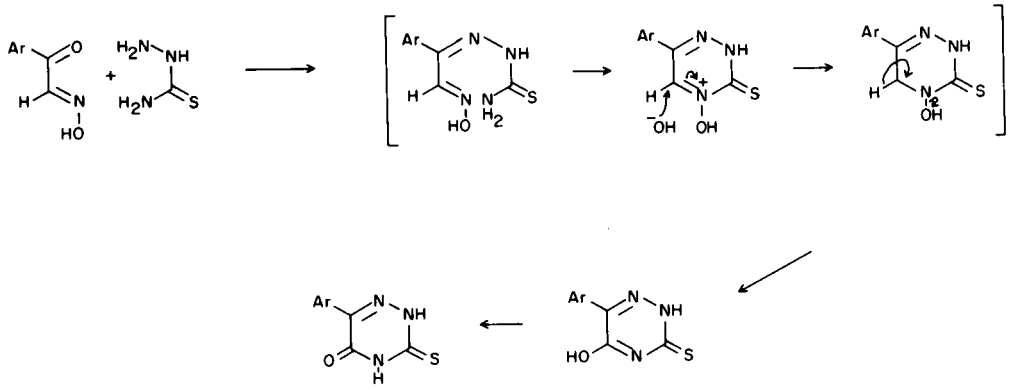
In continuation of our studies on base and acid-catalyzed cyclization of substituted glyoxalaldoxime semicarbazones, which led to the formation of 2,3,4,5-tetrahydro-*as*-triazine-3,5-diones (2,3), and 2,3-dihydro-*as*-triazine-3-ones (4), we wish to report one-step syntheses of 6-substituted-2,3,4,5-tetrahydro-*as*-triazin-5-one-3-thione (1), 6-phenyl-2,3-dihydro-*as*-triazine-3-thione and 3-pyrrolidino-6-phenyl-*as*-triazine.

Attempts to prepare substituted glyoxalaldoxime thiosemicarbazones failed. However substituted glyoxalaldoximes refluxed with thiosemicarbazide in aqueous alkaline solutions led to the formation of I.

Physical properties and chemical reactions of I showed that they were in fact the 6-substituted-2,3,4,5-tetrahydro-*as*-triazin-5-one-3-thione, identical with samples prepared by other methods (5,6). [Alkaline potassium permanganate oxidation of I afforded 6-substituted-2,3,4,5-tetrahydro-*as*-triazine-3,5-diones (2)].

Refluxing aqueous solutions of equivalent quantities of arylglyoxalaldoximes (as sodium salts) and thiosemicarbazide gave the best yields. No *as*-triazine separated in the total absence of alkali or where the reaction was

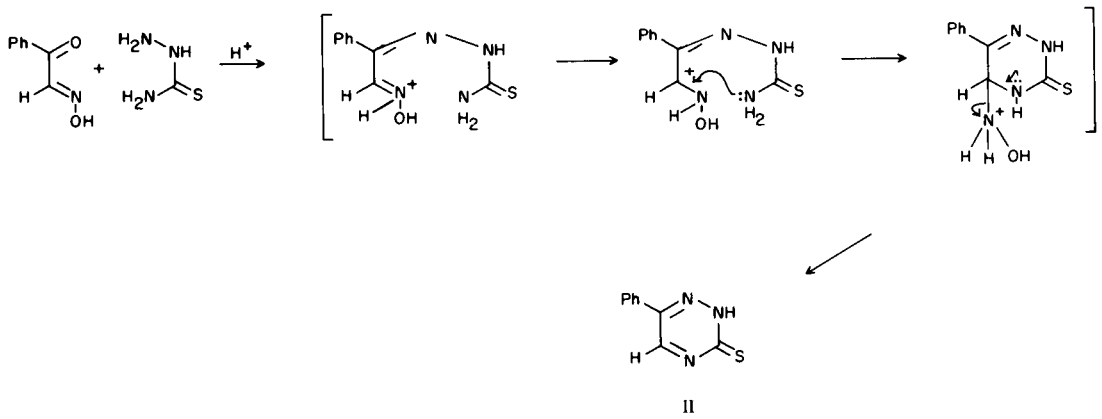
SCHEME I



I

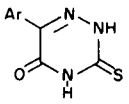
Ar = C_6H_5; *p*-FC_6H_4; *p*-ClC_6H_4; *p*-BrC_6H_4; *p*-$CH_3C_6H_4$; *p*-$CH_3OC_6H_4$; 2-thienyl; 3-pyridyl.

SCHEME II



II

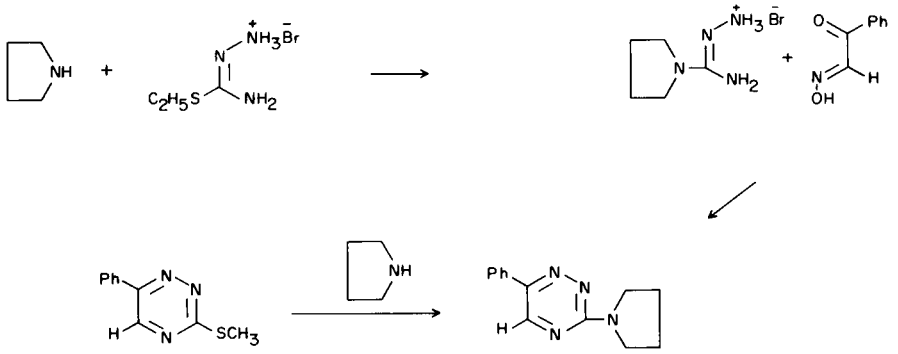
TABLE I



Ar	M.P. °C	Yield %	Formula	Percent C Calcd.	Percent C Found	Percent H Calcd.	Percent H Found
C_6H_5	265 (a)	58	$C_9H_7N_3OS$	52.68	52.73	3.41	3.33
p-FC_6H_4	249	35	$C_9H_6FN_3OS$	48.43	48.09	2.69	2.82
p-ClC_6H_4	273 (b)	65	$C_9H_6ClN_3OS$	45.09	45.02	2.50	2.46
p-BrC_6H_4	285 (c)	66	$C_9H_6BrN_3OS$	38.02	37.95	2.11	2.11
p-$CH_3C_6H_4$	258	28	$C_{10}H_9N_3OS$	54.79	54.82	4.10	4.20
p-$CH_3OC_6H_4$	272 (d)	31	$C_{10}H_9N_3O_2S$	51.06	51.23	3.82	3.99
2-Thienyl	279 (e)	15	$C_7H_5N_3OS_2$	39.81	40.04	2.36	2.41
3-Pyridyl	313 (f)	33	$C_8H_6N_4OS$	46.60	46.73	2.91	3.02

(a) lit. (5) 260°. (b) lit. (6) 288-290°. (c) lit. (6) 278-280°. (d) lit. (6) 278-280°. (e) lit. (6) 282-284°. (f) lit. (6) 336°.

SCHEME III



III

conducted in presence of sodium ethoxide. Small amounts of nitriles (5-10%) and acids (10-20%) based on the starting glyoxalaldoximes as well as ammonia were identified in these reactions.

On the basis of these observations and our previous work (3), the mechanism of formation of I is presumably that shown in Scheme I.

Recent investigations in the naphthotriazine series (7) favor an *N*-oxide intermediate as outlined in Scheme I. Compounds prepared by this method are listed in Table I.

When phenylglyoxalaldoxime and thiosemicarbazide were allowed to react in boiling water in the presence of a few drops of hydrochloric acid, 6-phenyl-2,3-dihydro-*as*-triazine-3-thione was obtained. A possible mechanism for this reaction is shown in Scheme II.

The nmr spectra of II showed a singlet (1H) at τ 1.2 characteristic of *as*-triazines with no substitution at position 5 (4). Further confirmation of the structure of II was obtained by the oxidative (hydrogen peroxide-acetic acid) transformation of the *S*-methyl derivative to 6-phenyl-2,3,4,5-tetrahydro-*as*-triazine-3,5-dione.

The *S*-methyl derivative of II refluxed with pyrrolidine in aqueous ethanol afforded 3-pyrrolidino-6-phenyl-*as*-triazine. This compound was also prepared by a one-step cyclization of 1-amino-3,3-tetramethyleneguanidinium bromide and phenylglyoxalaldoxime in acid medium as shown in Scheme III.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope and are uncorrected. The infrared spectra were determined

with a Leitz model spectrograph, using potassium bromide discs. The N.M.R. spectra were recorded on a varian A60A instrument.

6-Phenyl-2,3,4,5-tetrahydro-*as*-triazin-5-one-3-thione (I).

A solution of 3.42 g. (0.02 mole) of phenylglyoxalaldoxime (sodium salt) and 1.82 g. (0.02 mole) of thiosemicarbazide in 20 ml. of water was refluxed for 6 hours. The reaction mixture was steam distilled to remove the benzonitrile formed and after decolourizing with charcoal, it was acidified with acetic acid. The *as*-triazine which precipitated, was recrystallized from alcohol to give 2.3 g. (58%) of white microneedles.

The other compounds (I) were prepared in a similar way. The physical and analytical data are given in Table I.

6-Phenyl-2,3-dihydro-*as*-triazine-3-thione (II).

To a mixture of 1.49 g. (0.01 mole) of phenylglyoxalaldoxime and 0.91 g. (0.01 mole) of thiosemicarbazide in 15 ml. of water was added 5 drops of concentrated hydrochloric acid and refluxed for 2 hours. The light brown precipitate was filtered and recrystallized from dimethylsulfoxide to give 1.8 g. (95%) of light brown microneedles, m.p. 242°; ν max cm^{-1}, 3320, 3180, 3100, 1600, 1520, 1450, 1280, 1075, 855, 849, 710; NMR (deuteriochloroform), τ 1.5 (sharp s, 1H, CH), 2.2-2.7 (m, 5H, C_6H_5).

Anal. Calcd. for $C_9H_7N_3S$: C, 57.14; H, 3.70. Found: C, 57.22; H, 3.65.

3-Methylthio-6-phenyl-*as*-triazine.

Methyl iodide (1.56 g., 0.011 mole) was added to a solution of 1.8 g. (0.01 mole) of II in 25 ml. of 10% aqueous sodium hydroxide. After stirring one hour, the yellow precipitate was filtered, washed with water and recrystallized from alcohol to give 1.1 g. (54%) of yellow crystalline powder, m.p. 155°; NMR (deuteriochloroform), τ 7.45 (s, 3H, CH_3), 2.25-2.70 (m, 5H, C_6H_5), 10.5 (s, 1H, CH).

Anal. Calcd. for $C_{10}H_9N_3S$: C, 59.11; H, 4.43. Found: C, 59.23; H, 4.41.

6-Phenyl-2,3,4,5-tetrahydro-*as*-triazine-3,5-dione.

Method A.

A solution of 0.5 g. of I in 20 ml. of 5% aqueous sodium hydroxide was treated at room temperature with a saturated potassium permanganate solution until the pink color persisted. The excess of potassium permanganate was decomposed by alcohol and filtered. The solution was acidified to give a white precipitate which was recrystallized from dilute alcohol to give 0.46 g. (97%), m.p. 262° (lit. (2) 262°).

Method B.

A solution of 1 g. of 3-methylthio-6-phenyl-*as*-triazine in 20 ml. of acetic acid and 10 ml. of 30% hydrogen peroxide was heated for 6 hours on a steam bath and evaporated under reduced pressure. The residue was crystallized from dilute alcohol to give 0.67 g. (70%), m.p. 262°.

The compounds prepared by methods A and B were identical with an authentic sample prepared according to reference (2).

5,6-Dimethyl-2,3-dihydro-*as*-triazine-3-thione.

Diacetyl monoxime 3 g. (0.03 mole) and 2.7 g. (0.03 mole) of thiosemicarbazide was refluxed for ½ hour in 25 ml. of water containing 5 drops of hydrochloric acid. The reaction mixture was then filtered and washed with water and dried in an oven to obtain a substantially quantitative yield of a yellowish powder, m.p. 237° dec. (lit. (8) 233-237° dec.). The ir and nmr spectra of this compound were identical with an authentic sample (8).

Anal. Calcd. for $C_5H_7N_3S$: C, 42.55; H, 4.96. Found: C, 42.71; H, 5.03.

1-Amino-3,3-tetramethyleneguanidinium Bromide.

A solution of 10 g. (0.05 mole) of *S*-ethylthiosemicarbazidium bromide (9) and 5 ml. of pyrrolidine in 50 ml. of water was kept overnight at room temperature.

The reaction mixture was then evaporated in vacuum and the crystalline residue was recrystallized (ethanol-ethyl acetate) to give 8.7 g. (85%) of crystals, m.p. 178°.

Anal. Calcd. for $C_5H_{12}N_4 \cdot HBr$: C, 28.70; H, 6.22. Found: C, 29.02; H, 6.10.

3-Pyrrolidino-6-phenyl-*as*-triazine.

Method A.

1-Amino-3,3-tetramethyleneguanidinium bromide 2 g. (0.01 mole) and 1.5 g. (0.01 mole) of phenylglyoxalaldoxime in 20 ml. of water containing 1 ml. of hydrochloric acid was refluxed for 6 hours. The reaction mixture was filtered, made alkaline with ammonia to give a crystalline precipitate which after recrystallization from alcohol gave 1 g. (44%) of yellow plates, m.p. 175°.

Method B.

3-Methylthio-6-phenyl-*as*-triazine (2 g., 0.01 mole) and 2 ml. of pyrrolidine in 25 ml. of 80% alcohol was refluxed for 7 hours. The reaction mixture was then evaporated to dryness in vacuum and the residue was recrystallized from alcohol to give 1 g. (47%) of product, m.p. 175°; ν max cm^{-1}, 2950, 2800, 1850, 1535, 1100, 1030, 1010, 975, 805, 755, 690; NMR (deuteriochloroform), τ 8 (m, 4H, pyrrolidine), 6.3 (m, 4H, pyrrolidine), 2.25-2.70 (m, 5H, C_6H_5), 1.68 (s, 1H, CH).

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