# Selective Synthesis of 5- or 6-Phenyl-3-alkylamino-*as*-triazines

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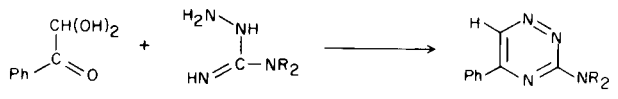
Received February 20, 1971

In a previous communication (1), we reported the synthesis of 6-aryl-3-amino-*as*-triazine by selenium dioxide oxidation of acetophenone guanylhydrazone. We have also demonstrated that alkyl or arylglyoxaldoxime semicarbazones cyclize in alkaline or acid medium to the corresponding 6-alkyl (or aryl)-2,3,4,5-tetrahydro-*as*-triazine-3,5-diones (2,3), or 6-aryl-2,3-dihydro-*as*-triazine-3-one (1), respectively. Similarly, treatment of arylglyoxaldoxime and thiosemicarbazide in alkali or acid medium led to the formation of 6-aryl-2,3,4,5-tetrahydro-*as*-triazine-5-one-3-thione and 6-aryl-2,3-dihydro-*as*-triazine-3-thione (4). 1-Amino-3,3-tetramethylenguanidinium bromide also reacted with phenylglyoxaldoxime in acid solution to give 6-phenyl-3-pyrrolidino-*as*-triazine (4). Other attempts (5) have shown that phenylglyoxal hydrate and aminoguanidinium chloride under specific conditions gives 5-phenyl-3-amino-*as*-triazine or mixtures of 5- and 6-phenyl-3-amino-*as*-triazines.

In the present work we are reporting two methods for the selective synthesis of 5-phenyl-3-alkylamino-*as*-triazine and three methods for the synthesis of their 6-phenyl analogues.

Phenylglyoxal hydrate and 1-amino-3-alkyl-guanidine in alkaline medium afforded a mixture of 5- and 6-phenyl-3-alkylamino-*as*-triazines (method A). However, the 5-isomer could be selectively prepared either by the reaction of 1-amino-3-alkyl-guanidine with phenylglyoxal hydrate in boiling acetic acid (method B) or refluxing the appropriate 1-amino-3-alkyl-guanidinium iodide and phenylglyoxal hydrate in aqueous solutions for a short period of time and then making them alkaline by addition of NaOH (method C).

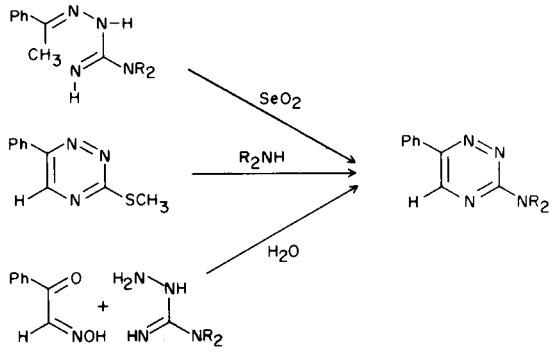


6-Phenyl-3-alkylamino-*as*-triazines were prepared by three independent methods:

D - Selenium dioxide oxidation of the corresponding acetophenon-3-alkyl-guanylhydrazone in acetic acid.

E - Aminolysis of 3-methylthio-6-phenyl-*as*-triazine.

F - Condensation of 1-amino-3-alkyl-guanidinium iodide with phenylglyoxaldoxime in acid medium.



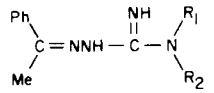
Acetophenon-1-amino-3-alkyl-guanylhydrazone used in method C was prepared either by heating an alkaline solution of the corresponding 1-amino-3-alkyl-guanidinium salt and acetophenone in aqueous ethanol, or warming 1-amino-3-alkyl-guanidinium iodide and acetophenone in glacial acetic acid.

The physical data of all the compounds prepared are summarized in Tables I and II.

Infrared and nmr spectra of the title *as*-triazines could be used for identification and differentiation between the 5- and 6-phenyl isomers. All 6-phenyl-3-alkylamino-*as*-triazines showed strong or medium intensity bands at 804-808 $cm^{-1}$ while their 5-phenyl isomers did not show absorption in this region.

Depending on their positions, 5 or 6-protons of the above *as*-triazines, have signals with different chemical shifts (see Table II).

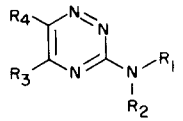
TABLE I



| $R_1$ | $R_2$ | Yield % | M.p. °C | Formula | C% Calcd. | C% Found | H% Calcd. | H% Found |
|---|---|---|---|---|---|---|---|---|
| H | $C_6H_5CH_2$ | 70 | 155-156 | $C_{16}H_{18}N_4$ | 72.15 | 72.86 | 6.76 | 6.75 |
| H | $C_2H_5$ | 65 | 85-85 | $C_{11}H_{16}N_4$ | 64.70 | 64.65 | 7.84 | 7.80 |
| $-(CH_2)_4-$ | | 73 | 91-93 | $C_{13}H_{18}N_4$ | 67.79 | 67.66 | 7.88 | 8.19 |
| $(CH_2)_2$-O-$(CH_2)_2$ | | 72 | 112-113 | $C_{13}H_{18}N_4O$ | 63.39 | 63.22 | 7.37 | 7.60 |
| $CH_3$ | $CH_3$ | 69 | 228-230 (a) | $C_{11}H_{16}N_4$ | 64.70 | 64.30 | 7.89 | 8.22 |

(a) As hydroiodide.

TABLE II



| No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Method of preparation | Yield % | M.p. °C | Formula | C% Calcd. | C% Found | H% Calcd. | H% Found | NMR Data $R_3$ = H | NMR Data $R_4$ = H |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | $C_2H_5$ | $C_6H_5$ | H | B | 56 | 133-134 (a) | $C_{11}H_{12}N_4$ | 66.00 | 66.09 | 6.00 | 5.86 | – | 9.00 |
| 2 | H | $C_6H_5CH_2$ | $C_6H_5$ | H | B | 48 | 153-154 (a) | $C_{16}H_{14}N_4$ | 73.28 | 73.31 | 5.34 | 5.42 | – | 9.10 |
| 3 | $CH_3$ | $CH_3$ | $C_6H_5$ | H | B | 52 | 85-89 (b) | $C_{11}H_{12}N_4$ | 66.00 | 65.90 | 6.00 | 6.06 | – | 9.00 |
| 4 | $(CH_2)_4$ | | $C_6H_5$ | H | A, B (d) | 43 | 95-97 (b) | $C_{13}H_{14}N_4$ | 69.02 | 69.09 | 6.19 | 6.16 | – | 8.90 |
| 5 | $(CH_2)_2$-O-$(CH_2)_2$ | | $C_6H_5$ | H | C | 48 | 105-108 (a) | $C_{13}H_{14}N_4O$ | 64.45 | 64.68 | 5.78 | 5.99 | – | 9.10 |
| 6 | H | $C_2H_5$ | H | $C_6H_5$ | D | 59 | 133-134 (c) | $C_{11}H_{12}N_4$ | 66.00 | 66.09 | 6.00 | 5.88 | 8.23 | – |
| 7 | H | $C_6H_5CH_2$ | H | $C_6H_5$ | D | 73 | 135-137 (a) | $C_{16}H_{14}N_4$ | 73.28 | 73.12 | 5.34 | 5.41 | 8.12 | – |
| 8 | $CH_3$ | $CH_3$ | H | $C_6H_5$ | D | 69 | 115-117 (b) | $C_{11}H_{12}N_4$ | 66.00 | 65.89 | 6.00 | 6.08 | 8.28 | – |
| 9 | $-(CH_2)_4-$ | | H | $C_6H_5$ | D, E (d), F | 56 | 175-176 (c) | $C_{13}H_{14}N_4$ | 69.02 | 69.21 | 6.19 | 6.21 | 8.32 | – |
| 10 | $(CH_2)_2$-O-$(CH_2)_2$ | | H | $C_6H_5$ | D, E (d), F | 71 | 123-124 (a) | $C_{13}H_{14}N_4O$ | 64.45 | 64.06 | 5.78 | 5.59 | 8.22 | – |

Solvent of crystallization: (a) ethanol, (b) ether-petroleum ether, (c) ethanol-water. (d) Yields given refer to these methods of preparation.

## EXPERIMENTAL

Acetophenone 3-Alkyl-guanylhydrazones.

To a mixture of 0.1 mole of the appropriate 3-alkyl-guanylhydrazinium salt, 0.1 mole of acetophenone and 0.2 mole of sodium hydroxide, enough alcohol was added to obtain a clear solution. After 3 hours heating on a water bath and cooling, the crystalline mass was filtered and recrystallized from alcohol-water (see Table I).

A. Mixture of 5 and 6-Phenyl-3-alkylamino-*as*-triazine.

When a mixture of molar quantities of phenylglyoxal hydrate and the appropriate 1-amino-3-alkyl-guanidium salt and 2 moles of sodium hydroxide in aqueous ethanol was refluxed for 2 hours and treated as above, a mixture of 5 and 6-phenyl-3-alkylamino-*as*-triazines was obtained. The separation of the two isomers were effected by tlc (silica gel, chloroform). The fast moving fraction was the 6-phenyl isomer.

B. 3-Morpholino-5-phenyl-*as*-triazine.

To a solution of 2.72 g. (0.01 mole) of *N*-aminoamidinomorpholinium iodide and 0.4 g. (0.01 mole) of sodium hydroxide in 5 ml. of water was added 10 ml. of acetic acid and 1.4 g. (0.01 mole) of phenylglyoxal hydrate. The mixture was refluxed for ½ hour. After dilution with water and cooling, the precipitate was collected and crystallized from ethanol to give 1.16 g. (48%) of 5, m.p. 105-108°.

C. General Procedure of Preparation of 3-Alkylamino-5-phenyl-*as*-triazine.

A mixture of phenylglyoxal hydrate (0.01 mole) in 7 ml. of alcohol and 0.01 mole of the appropriate 3-alkyl-guanylhydrazinium salt in 7 ml. of water was refluxed for a few minutes and 0.05 mole of sodium hydroxide in 2 ml. of water was added and refluxing was continued for 10 minutes. To the cold solution, water was added and the triazine was extracted with chloroform. After removing the solvent, the residue was purified by tlc (silica gel, chloroform) (see Table II).

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

General Procedures.

D. Selenium Dioxide Oxidation of Acetophenone 3-Alkyl-guanylhydrazones.

Selenium dioxide (0.011 mole) and 0.01 mole of the appropriate acetophenone 3-alkyl-guanylhydrazone in 15 ml. of acetic acid was refluxed for 3 hours. The reaction mixture was diluted with water, extracted with chloroform, neutralized with sodium bicarbonate, washed with water and dried. After removing the solvent, the residue was purified by tlc (silica gel, chloroform) (see Table II).

E.

A solution of 1-amino-3-alkyl-guanidinium salt (0.01 mole) and phenylglyoxaldoxime (0.01 mole) 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 was recrystallized from the appropriate solvent (see Table II).

F.

A solution of 3-methylthio-6-phenyl-*as*-triazine (4) (0.01 mole) and 2 ml. of the appropriate amine in 25 ml. of 80% alcohol was refluxed for 7 hours. The reaction mixture was evaporated to dryness in vacuum and the residue was recrystallized (see Table II).

Acknowledgment.

We are indebted to Dr. A. N. Alikhani for his constant encouragements and to Dr. M. L. Smith of the Central Treaty Organization for the supply of essential materials.

## REFERENCES

(1) I. Lalezari, N. Sharghi, A. Shafiee and M. Yalpani, *J. Heterocyclic Chem.*, **6**, 403 (1969).

(2) I. Lalezari, *J. Org. Chem.*, **33**, 4281 (1968).

(3) I. Lalezari, A. Shafiee and M. Yalpani, *Tetrahedron Letters*, **36**, 3059 (1969).

(4) I. Lalezari and H. Golgolab, *J. Heterocyclic Chem.*, **7**, 689 (1970).

(5) J. A. Elvidge, G. T. Newbold, I. R. Senciall and T. G. Symes, *J. Chem. Soc.*, 4157 (1964).