[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

New 1,2,4-Triazine Derivatives[1a]

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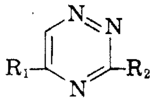
3,5-Dichloro-1,2,4(*as*-)-triazine has been prepared by chlorination of the corresponding 3,5-dioxytriazine. By reaction of the dichloro-*as*-triazine with several nucleophilic reagents, a number of new simple mono- and disubstituted *as*-triazine derivatives were obtained. Neither the dehalogenation of 3,5-dichloro-*as*-triazine nor the hydrogenolysis of 3,5-dithiomethyl-*as*-triazine to the parent compound was possible.

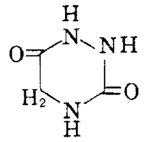
Although a considerable number of 1,2,4-(or *as*-)-triazine derivatives have been prepared, especially during the last decade, the underlying parent compound of this heterocyclic system is still unknown. The closest homologs, known so far, are lower aliphatic di- and trisubstituted *as*-triazines.[2] The methods which led to their synthesis are apparently not applicable for the preparation of the parent compound. An attempt to obtain *as*-triazine by oxidative degradation of the above mentioned alkyl-*as*-triazines resulted in complete destruction of the *as*-triazine ring by the employed oxidants.[3]

The 3,5-dichloro-1,2,4-triazine was considered as a potential starting material for new simple *as*-triazines, including the parent compound. The 3,5-dihydroxy-*as*-triazine[4] (I) or its sodium salt could be converted by means of "aged" phosphorus oxychloride and triethylamine[5] into the desired 3,5-dichloro-*as*-triazine (II) which was found to be much more sensitive than the corresponding isomer of the *s*-triazine series.[6] The reactivity of the chlorine atoms of II was established by reaction of II with a number of nucleophilic reagents, such as alcohols, mercaptans, and amines. Alcoholic ammonia replaced easily one chlorine atom at room temperature, leading to 3-amino-5-chloro-*as*-triazine (III).[7] With dimethylamine and ethyleneimine 5-chloro-3-dimethylamino-*as*-triazine (IV) and 3-aziridino-5-chloro-*as*-triazine (V), respectively, were obtained. Although IV acted to a minor degree as a catalyst poison, it could be hydrogenolyzed to 3-dimethylamino-*as*-triazine (VI). The second chlorine atom of II is much tighter bound, an attempt to react III with ammonia at 130° resulted in destruction of the *as*-triazine ring.

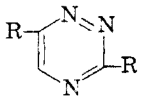
Sodium ethylate replaced the chlorine atom in the 5-position of IV easily, leading to 3-dimethylamino-5-ethoxy-*as*-triazine (VII). Adding II to an alcoholic solution of sodium methylmercaptide at room temperature resulted in 3-ethoxy-5-thiomethyl-*as*-triazine (VIII). When the procedure was reversed, a moderate yield of 3,5-bisthiomethyl-*as*-triazine (IX) was obtained, while the same reaction in xylene proceeded stepwise, leading first to 5-chloro-3-thiomethyl-*as*-triazine (X) and finally to IX. Based on experiences in the *s*-triazine series[8] it was hoped to achieve hydrogenolysis of IX with Raney nickel to *as*-triazine. This technique, however, led in this case to extensive fargoing hydrogenolysis. Likewise, all attempts to dehalogenate II to the parent compound, *as*-triazine, with hydrogen and noble metal catalysts failed.



	R_1 =	R_2 =
I	OH	OH
II	Cl	Cl
III	Cl	NH_2
IV	Cl	NMe_2
V	Cl	$N(CH_2)_2$
VI	H	NMe_2
VII	EtO	NMe_2
VIII	MeS	EtO
IX	MeS	MeS
X	Cl	MeS



XI



XII R = OH
XIII R = Cl

The isomer of I, 3,6-dihydroxy-*as*-triazine (XII) was prepared from the corresponding dihydro compound (XI)[9] by dehydrogenation with bromine. Unlike I, XII could not be converted into the desired 3,6-dichloro-*as*-triazine (XIII).

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[2] R. Metze, *Chem. Ber.*, **88**, 772 (1955).

[3] R. Metze and S. Meyer, *Chem. Ber.*, **90**, 481 (1957).

[4] W. Seibert, *Chem. Ber.*, **80**, 494 (1947).

[5] This reagent was first found useful in the difficult conversion of 2,4-dimethyl-6-hydroxy-*s*-triazine into the chloro compound, *cf.* H. Schroeder and Ch. Grundmann, *J. Am. Chem. Soc.*, **78**, 2447 (1956).

[6] Ch. Grundmann and E. Beyer, *J. Am. Chem. Soc.*, **76**, 1948 (1954); I. Hechenbleikner, *J. Am. Chem. Soc.*, **76**, 3032 (1954).

[7] From analogy with the corresponding derivatives of the pyrimidine series we may assume that the chlorine atom in 3-position is more reactive than that in 5-position, but this is not strictly proven. This is valid for all unsymmetrical 3,5-disubstituted *as*-triazines prepared from II.

[8] Ch. Grundmann, H. Ulrich, and A. Kreutzberger, *Chem. Ber.*, **86**, 181 (1953); Ch. Grundmann and E. Kober, *J. Org. Chem.*, **21**, 641 (1956).

[9] A. Lindenmann, N. H. Khan, and K. Hofmann, *J. Am. Chem. Soc.*, **74**, 476 (1952).

EXPERIMENTAL[10]

3,5-Dihydroxy-as-triazine (I). Ethyl semicarbazinoacetate was prepared according to Bailey and Read.[11] According to these authors treatment of this compound with sodium ethanolate produces the monosodium salt of 3,5-dihydroxy-1,6-dihydro-1,2,4-triazine (Ia). Working with 1.5 moles of sodium in 96% ethanol we obtained the dihydrate of a disodium salt of Ia in 75% yield.

Anal. Calcd. for $C_3H_7N_3Na_2O_4$: N, 21.54, Na, 23.57. Found: N, 21.30, 21.18, Na, 23.59, 23.46.

The free dihydroxydihydro-*as*-triazine (Ia) was obtained with a 75% yield by precipitation from the solution of the disodium salt in diluted hydrochloric acid with the double amount of ethanol, m.p. 234° (lit. 221°).

Anal. Calcd. for $C_3H_5N_3O_2$: C, 31.30, H, 4.38, N, 36.51. Found: C, 31.41; H, 3.69; N, 36.89.

Metze[12] reported recently this conversion to be very difficult, producing only minute yields of Ia when following the procedure of Bailey and Read.

Oxidation of 3,5-dihydroxy-1,6-dihydro-1,2,4-triazine to I: A solution of 17 g. of bromine in 600 ml. of H_2O was added to the solution of 11.5 g. of the dihydro compound in 600 ml. of H_2O at 25°. The slightly yellow solution was evaporated *in vacuo* to 120 ml. and 11 g. of I (98%) precipitated upon cooling, m.p. 278°.

I had been obtained previously by Seibert[4] from its sodium salt which resulted from the reaction of glyoxylic acid semicarbazone with 2*N* NaOH. Since he did not give the yield nor the constitution of the salt we checked his procedure and found that the disodium-3,5-dihydroxy-1,2,4-triazine is formed in a 27.5% yield.

Anal. Calcd. for $C_3HN_3Na_2O_2$: N, 26.76; Na, 29.28. Found: N, 26.68, 26.72; Na, 30.33, 30.41.

I was characterized by methylation with diazomethane. The main product of this reaction was a dimethyl derivative, crystallizing from petroleum ether in large crystals, m.p. 55°.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.60; H, 4.96; N, 29.80. Found: C, 42.36; H, 4.98; N, 29.65.

A minor part of the reaction product was completely insoluble in petroleum ether, m.p. 164–165°. According to its analytical data it is a monomethyl derivative of I.

Anal. Calcd. for $C_4H_5N_3O_2$: C, 37.81; H, 3.93; N, 33.05. Found: C, 38.45; H, 4.06; N, 32.89.

3,5-Dichloro-as-triazine (II). A mixture of 5 g. of disodium-3,5-dihydroxy-1,2,4-triazine, 40 g. of "aged $POCl_3$," and 6 g. of triethylamine was refluxed for 40 min. Then the excess $POCl_3$ was removed at reduced pressure. II started to distil (or partially to sublime) into the condenser at 80° and 1 mm. The operation was stopped as soon as the bath had reached a temperature of 140°. The reaction product was extracted with petroleum ether and crystallized from the concd. solution. The yellowish product was recrystallized again from petroleum ether to give long, white needles of II (500 mg., 10.4%), m.p. 55°. The same yield was obtained with I instead of its disodium salt.

Anal. Calcd. for $C_3HCl_2N_3$: C, 24.02; H, 0.67; Cl, 47.28; N, 28.02. Found. C, 24.22, 24.42; H, 0.75, 0.78; Cl, 47.22, 47.00; N, 27.51, 27.45.

II had to be kept in the refrigerator with exclusion of moisture, even then it started slowly to decompose after several days. Due to the reactivity of the chlorine atom in the 3-position II hydrolyzed easily; it also reacted with tertiary bases, *e.g.*, triethylamine, to form a solid, probably a quaternary ammonium salt.

Much effort was spent on attempts to dehalogenate II catalytically by means of hydrogen and palladium-charcoal in different solvents with or without addition of scavengers for the formed hydrogen chloride (MgO; $Me_2N \cdot Ph$). In ether or petroleum ether no hydrogen absorption at all could be observed, even under pressures up to 450 p.s.i. The reason for this inertness is the poisoning effect of II on noble metal catalysts. This was proved by the inhibition of the reduction of cyclohexene with the same catalyst in presence of very small amounts of II. In methanol, however, especially in presence of bases a rapid uptake of two moles of hydrogen was observed. But the resulting product could not be expected to represent the desired *as*-triazine, since it was found that II reacted easily with methanol alone under these conditions. Treatment of the reaction product with hot water or nitric acid converted it back into I. Accordingly, the obtained amorphous hydrogenation product must be a derivative of I, possibly a dimethoxy- or methoxy-chloro-tetrahydro-*as*-triazine.

3-Amino-5-chloro-as-triazine (III). An amount of 350 mg. of II was added with stirring to 15 ml. of a 10% solution of ammonia in ethanol. After evaporation of the excess ammonia and ethanol, the residue was recrystallized from water (150 mg., 49%). On the melting point apparatus it started to turn dark around 205° and was completely decomposed at 250°.

Anal. Calcd. for $C_3H_3ClN_4$: C, 27.60; H, 2.32; Cl, 27.16; N, 42.92. Found: C, 27.21, 27.11; H, 2.99, 3.06; Cl, 26.84, 26.80; N, 42.87, 42.81.

The reaction of II with alcoholic ammonia at 130° in a sealed tube did not lead to the desired 3,5-diamino-*as*-triazine, but yielded a compound, $C_4H_{15}Cl_3N_8$, m.p. 290°, of still undetermined structure.

Anal. Calcd. for $C_4H_{15}Cl_3N_8$: C, 17.06; H, 5.37; Cl, 37.77; N, 39.80. Found: C, 16.81, 16.74; H, 5.02, 5.00; Cl, 37.49, 37.31; N, 39.40, 39.35.

5-Chloro-3-dimethylamino-as-triazine (IV). The solution of 300 mg. of II in 5 ml. of benzene was added with stirring to 10 ml. of a 15% solution of dimethylamine in benzene. After 5 min. dimethylamine·HCl was filtered off and the filtrate was evaporated under reduced pressure. The remaining IV (170 mg., 53.6%) was recrystallized from CCl_4 and from ligroine, m.p. 119°.

Anal. Calcd. for $C_5H_7ClN_4$: C, 37.86; H, 4.45; Cl, 22.36, N, 35.33. Found: C, 37.94, 38.08, H, 4.39, 4.62; Cl, 22.32; 22.31; N, 35.25, 35.16.

3-Aziridino-5-chloro-as-triazine (V). A solution of 300 mg. of II in 10 ml. of ether was dropped with stirring to 500 mg. of ethylenimine in 10 ml. of ether. The ethyleneimine hydrochloride separated as a solid but changed to a heavy oil after 3 min. The ether solution was decanted and evaporated *in vacuo*, then the residual solid was recrystallized twice from ligroine. Yield of V: 120 mg. (38.4%); m.p. 95°.

Anal. Calcd. for $C_5H_5ClN_4$: C, 38.35; H, 3.22; Cl, 22.65; N, 35.78. Found: C, 38.39, 38.51; H, 3.23, 3.16; Cl, 22.60, 22.81; N, 35.52, 35.37.

3-Dimethylamino-as-triazine (VI). A mixture of 240 mg. of IV, 152 mg. of triethylamine, 0.6 g. of a 10% Pd-on-carbon catalyst, and 25 ml. of benzene was shaken with hydrogen under atmospheric pressure. One mole equivalent of H_2 was absorbed in 4 min. Then the catalyst and the triethylamine·HCl formed in the reaction was filtered off and the filtrate was evaporated *in vacuo*. Recrystallization of the remaining VI from ligroine gave 80 mg. (42.5%), m.p. 108°.

Anal. Calcd. for $C_5H_8N_4$: C, 48.37; H, 6.50; N, 45.13. Found: C, 48.36; H, 6.63; N, 44.98.

3-Dimethylamino-5-ethoxy-as-triazine (VII). A solution of 50 mg. of sodium metal (15% excess) in 3 ml. of absolute ethanol was added with stirring and ice-cooling to the solution of 300 mg. of IV in 10 ml. of absolute ethanol. After keeping the mixture at 25° for 30 min., the ethanol was

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[10] All melting points are determined with the Fisher-Johns apparatus, microanalyses are from Galbraith Laboratories, Knoxville, Tenn., and Spang Microanalytical Laboratory, Ann Arbor, Mich.

[11] J. R. Bailey and W. T. Read, *J. Am. Chem. Soc.*, **36**, 1747 (1914).

[12] R. Metze, *Wissensch. Zeitschr. d. Humboldt Universitaet Berlin* **II**, (Math. Nat. Reihe No. 3/4), 37 (1952/1953).

evaporated and the reaction product was extracted with hot ligroine (135 mg., 43%), m.p. 78–79°.

Anal. Calcd. for $C_7H_{12}N_4O$: C, 50.28; H, 6.63; N, 33.51. Found: C, 50.30, 50.21; H, 7.01, 7.12; N, 33.11, 33.07.

3-Ethoxy-5-thiomethyl-as-triazine (VIII). A solution of 2.572 g. of II in 50 ml. of ice cold absolute ethanol was added in 30 min. to the solution of 0.828 g. of Na in 35 ml. of ethanol and 10 ml. of methanethiol. After standing for 2 hr. at room temperature, the reaction mixture was evaporated at 40° and the residual product was extracted with petrol ether. After evaporating the filtrate, 1.99 g. of a product, melting at 37–43°, was obtained which was recrystallized twice from petrol ether (1.68 g., 57.5%), m.p. 41–42°.

Anal. Calcd. for $C_6H_9N_3OS$: C, 42.34; H, 4.74; N, 24.69; S, 18.84. Found: C, 42.33; H, 5.06; N, 24.41; S, 18.87.

3,5-Bisthiomethyl-as-triazine (IX). A 200-ml. four-neck flask, fitted with an air-driven stirrer, gas-inlet tube, dropping funnel, and condenser with drying tube, was placed in a Dewar-vessel and chilled to −20°. Then 125 g. of methanethiol and 3 g. of metallic sodium wire, cut under *n*-heptane into small pieces, was added. With moderate stirring and passing a slow N_2 stream over the surface of the methanethiol, the mixture was allowed to stand overnight. After 12 hr. 400 ml. of sodium dried xylene was added to the almost black reaction mixture through the dropping funnel. With stirring and under nitrogen the dark suspension was heated within 1 hr. to 45°. Above this temperature the conversion of the dark material[13] (probably an addition product of Na with CH_3SH) into sodium methylmercaptide started with heavy foaming and was complete within a few minutes. After cooling to room temperature, 6 g. of II dissolved in 100 ml. of xylene was added dropwise with stirring. The reaction was completed by heating for 2 hr. at 70° and 1 hr. standing at room temperature. The salts were filtered off and the solvent carefully removed from the filtrate *in vacuo* at 40°. The solid residue was then extracted with 700 ml. of petrol ether. After concentration of the solution to one third of its original volume, VIII crystallized at −15° in compact crystals (5.34 g., 77%), m.p. 57°.

Anal. Calcd. for $C_5H_7N_3S_2$: C, 34.66; H, 4.07; N, 24.26; S, 37.01. Found: C, 34.89; H, 4.14; N, 24.09; S, 36.89.

VIII was more conveniently prepared by adding a solution of Na in ethanol and methanethiol to a solution of II in cold ethanol and repeated recrystallization of the reaction product from petrol ether with charcoal, but the yield dropped in this case to 26%.

Raney nickel reacted spontaneously at room temperature with VIII in ligroine and also in petrol ether. On refluxing, however, an evolution of ammonia was observed, apparently due to a fargoing decomposition of the molecule. Work-up of the reaction mixture gave in each case a pasty basic product with an amine-like odor which formed in alcoholic solution in a small yield a crystalline picrate; m.p. 256° after recrystallization from water.

Anal. Calcd. for $C_{11}H_{16}N_4O_7$: C, 41.77; H, 5.01; N, 17.72. Found: C, 41.72, 41.93; H, 5.16, 4.93; N, 17.79, 17.94; S, 0.0.

The structure of the underlying base $C_5H_{13}N$ was not determined, by comparison with an authentic specimen it was found not to be identical with the picrate of ethyl-isopropylamine[14] whose formation would be conceivable under the reaction conditions.

5-Chloro-3-thiomethyl-as-triazine (X). An amount of 0.175 g. of sodium was dissolved in 40 g. of methanethiol with stirring at −20° within 24 hr. After addition of 50 ml. of xylene and refluxing the mixture for 2 hr., 0.529 g. of II in 10 ml. of xylene was added. The reaction mixture was kept at 25° for 2 hr. After removing the xylene *in vacuo* the reaction product was extracted with petrol ether. An oily by-product was removed by a second recrystallization from petrol ether with charcoal (180 mg., 32%), m.p. 99°.

Anal. Calcd. for $C_4H_3ClN_3S$: C, 29.91; H, 1.81; N, 26.17; S, 19,96. Found: C, 29.68; H, 2.31; N, 26.50; S, 19.46.

3,6-Dihydroxy-as-triazine (XII). To the solution of 10 g. of 3,6-dihydroxydihydro-1,2,4-triazine (XI) in 400 ml. of H_2O was added with shaking the solution of 15 g. of bromine 400 ml. of H_2O. In spite of some unreacted bromine still present, the precipitate was filtered off, washed with ethanol and ether, and purified from traces of adhering bromine by treatment with diazomethane in ether which did not methylate IX in contrast to our results with 3,5-dihydroxy-1,2,4-triazine (I), Yield of IX: 3.9 g. (39.4%), m.p. 266°.

Anal. Calcd. for $C_3H_3N_3O_2$: C, 31.86; H, 2.67; N, 37.16. Found: C, 32 .00; H, 2.69; N, 37.08.

All attempts to chlorinate IX to 3,6-dichloro-1,2,4-triazine (XI) using "aged $POCl_3$" and pyrophosphoryl chloride in presence of amines, like triethylamine and diethylaniline, gave only black tars without any distillable product.

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(13) Because of the highly pyrophoric nature of this material, this experiment is definitely dangerous, if not carried out exactly as described!

(14) A. Schuftan, Ber., **27**, 1009 (1894).