Appendix

ENERGY LEVELS AND COEFFICIENTS OF ATOMIC ORBITALS FOR MOLECULAR ORBITALS OF THIOPHENE AND 1,4-DITHIADIENE

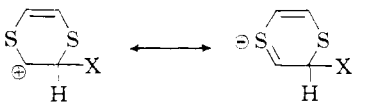
	E	C_1	C_2	C_3	C_4	C_5	C_6
				Thiophene			
1	$+1.930\beta$	0.428	0.439	0.465	0.465	0.439	
2	$+0.531\beta$	.663	.187	− .496	− .496	.187	
3	-1.571β						
4	$+0.691\beta$	.000	.593	.386	− .386	− .593	
5	-1.621β						
				1,4-dithiadiene			
1	$+1.88\beta$	0.354	0.432	0.432	0.354	0.432	0.432
2	-0.82β	.564	− .300	− .300	.564	− .300	− .300
3	-1.06β						
4	$+1.06\beta$	.000	+ .500	+ .500	.000	− .500	− .500
5	$+0.82\beta$	+ .564	+ .300	− .300	− .564	− .300	+ .300
6	-1.88β						

quantitatively applied to heterocyclic compounds, it has been indicated that these should not differ too much from related hydrocarbons.[33]

The free valence and localization energy of thiophene fit in with the above generalizations nicely, the localization energy (2.45β) being a bit smaller than that for benzene (2.54β) while the free valence (0.43) is a bit larger. In calculating the resonance energy of thiophene after attack by a radical, the resonance integral was assumed to be 1.00β for all adjacent atoms since the exact geometry is unknown. For the same reason strain was assumed to be the same as in the parent molecule. Unfortunately the methyl affinity of thiophene does not seem to be known, but the calculations give no reason to think that it would be other than slightly higher than that for benzene.

The same thing is not true for 1,4-dithiadiene. While the free valence for the carbon atoms of this compound is intermediate between those of benzene and those of ethylene, its localization energy (1.42β) is much less than either. The approximations as to geometry and resonance integrals were the same as those mentioned for thiophene, causing some uncertainty as to the exact value of localization energy, but it is so much lower than that of any compound previously studied that the qualitative prediction cannot be altered in any reasonable way. If the linear relation between the log of the methyl affinities and the localization energies holds, the methyl affinity of 1,4-dithiadiene should be 10^7 times that of benzene!

Even more striking is the small loss in resonance energy calculated for 1,4-dithiadiene when it reacts with a positively charged species. The resultant ion has a calculated resonance energy only 0.42β less than that of the parent compound.



The same approximations for resonance integrals and strain mentioned above are involved here, but no reasonable set of approximations can bring the value even close to the 2.53β calculated loss of resonance energy for benzene in a similar process or the 2.00β for ethylene or even the 1.83β calculated loss for thiophene. The comparatively tiny calculated loss for 1,4-dithiadiene indicates that this compound should be *much* more basic than benzene or thiophene. It also strongly suggests that 1,4-dithiadiene should be very susceptible to attack by electrophilic reagents.

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[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Triazines. XXI. The Preparation of s-Triazine Aldehydes[1,2]

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Several hydrazones of 4,6-disubstituted s-triazine aldehydes were obtained by reduction of the corresponding 4,6-disubstituted 2-diazomethyl-s-triazines with hydrogen sulfide or alkylthiols. These hydrazones could be cleaved to the free s-triazine aldehydes. The properties of two of these aldehydes are described. A number of unsuccessful attempts to prepare s-triazine aldehydes by conventional routes are discussed briefly.

Although much work has been done in the last years in the s-triazine series, s-triazine aldehydes are still unknown. Oximes of substituted tetrahydro-s-triazine aldehydes have been prepared, but not the free aldehydes.[3] Likewise, attempts to hydrolyze

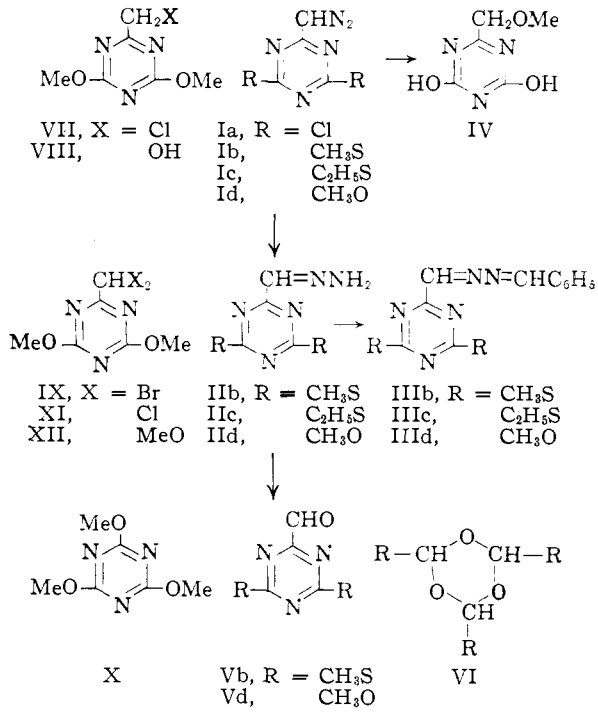
(1) This article is based on work performed under project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, New York, N. Y.

(2) Preceding communication: Ch. Grundmann and A. Kreutzberger, THIS JOURNAL, **80**, in press (1958).

(3) A. Ostrogovich and V. Crasu, *Gazz. chim. ital.*, **64**, 800 (1934); **66**, 653 (1936); A. Ostrogovich and J. Cadariu, *ibid.*, **71**, 505, 515, 524 (1941).

some acetals of the 2,4-diamino-*s*-triazine-6-aldehyde met with failure.[4]

This paper deals with a novel route to *s*-triazine aldehydes, starting with the recently described diazomethyl-*s*-triazines (I).[5] These compounds could be reduced selectively to the corresponding hydrazones of the *s*-triazine aldehydes (II) by means of hydrogen sulfide or preferably by lower alkyl thiols. The mercaptans were thereby converted into the corresponding dialkyl disulfides.[6]



The reaction proceeds satisfactorily in an alkaline or neutral medium, preferably in the presence of lower alcohols as solvents. Diazomethyl-*s*-triazines containing reactive halogen atoms in the 4- and 6-positions will undergo subsequent changes. For instance, 2-diazomethyl-4,6-dichloro-*s*-triazine (Ia) reacted with an excess of methanethiol or ethanethiol in the presence of two moles of sodium alkoxide to give the 4,6-bis-thiomethyl- and 4,6-bis-thioethyl-*s*-triazine-2-aldehyde hydrazones (IIb and IIc). When Ia was treated with methanethiol in methanol without adding alkali, the reaction product was 4,6-dihydroxy-2-methoxymethyl-*s*-triazine (IV). Obviously the free hydrogen chloride, released during the reaction, converted the diazomethyl group of Ia into a methoxymethyl group before reduction could take place. With these limitations the reduction of diazomethyl-triazines by hydrogen sulfide or alkylthiols seems to be a satisfactory general method for the preparation of *s*-triazine aldehyde hydrazones.

The substituted *s*-triazine aldehyde hydrazones IIb-d were thus prepared from the corresponding diazomethyl compounds Ib-d. The aldehyde hydrazones IIb-d were characterized by the condensation with benzaldehyde to the well crystallized, yellow colored, mixed azines IIIb-d.

Contrary to the oximes of Ostrogovich, *et al.*,[3] the hydrazones of the triazine aldehydes could be successfully hydrolyzed to the corresponding free aldehydes. The sensitivity of the substituents in 4- and 6-position as well as of the *s*-triazine ring in general to acids forbade the application of acid hydrolysis. Among the other possibilities studied, the cleavage of the hydrazones with 2,4-dinitrobenzaldehyde proved most satisfactory. The free aldehydes Vb and Vd could be so obtained in satisfactory yield. Both aldehydes are crystalline solids, characterized by the easy formation of relatively stable crystalline hydrates. They display the conventional color reactions for the detection of aldehydes, *e.g.* the Fehling, Angeli-Rimini and Schiff reaction. At room temperature they seem not to be autoxidable, but polymerize slowly within several months. These crystalline polymers are characterized by their insolubility in all common organic solvents at ordinary temperature and by the ease with which they depolymerize to the monomers Vb resp. Vd.,when heated with a suitable solvent. They might probably have a trioxane structure (VI), often encountered in this type of polymeric aldehyde. The monomeric aldehydes Vb and Vd form well crystallized derivatives with the usual aldehyde reagents. With respect to their similarity to known active members of pyridine series, the thiosemicarbazones of Vb and Vd were tested as tuberculostatics, but failed to display any significant activity.

Attempts to oxidize directly the diazomethyl-*s*-triazines[5] to the *s*-triazine aldehydes by lead tetraacetate, selenium dioxide and perbenzoic acid failed. The direct oxidation of methyl-*s*-triazines with reagents like nitric acid, chromic acid and selenium dioxide did not lead to the desired aldehydes. Some starting materials, like 2-methyl-*s*-triazine itself, 2,4,6-trimethyl-*s*-triazine and 4,6-dichloro-2-methyl-*s*-triazine, were too sensitive against hydrolysis to permit the isolation of other products than those of fargoing degradation. Other methyl-*s*-triazines like 4,6-bis-trichloromethyl-2-methyl-*s*-triazine were not attacked at all,[7] while in the case of 4,6-diphenyl-2-methyl-*s*-triazine the oxidation went always directly to the corresponding acid. The 4,6-diphenyl-2-methyl-*s*-triazine also did not condense with *p*-nitrosodimethylaniline in the presence of potassium carbonate or sodium methylate.

By our previous work several halogenomethyl-, hydroxymethyl- and bis-halogenomethyl-*s*-triazines have become easily accessible.[5] Following the indications of recent German Patents,[8] sodium nitrocyclohexane was treated with 2-chloromethyl-4,6-dimethoxy-*s*-triazine (VII) in order to obtain the 4,6-dimethoxy-*s*-triazine-2-aldehyde (Vd). The reaction, however, took another course, leading to two still unidentified *s*-triazine derivatives, described in detail in the Experimental part. Likewise the Sommelet reaction with VII produced the

(4) V. P. Wystrach and J. G. Erickson, THIS JOURNAL, **75**, 6345 (1953).

(5) Ch. Grundmann and E. Kober, *ibid.*, **79**, 944 (1957).

(6) A similar observation has been made earlier in the case of diazoacetophenone; L. Wolff, *Ann.*, **394**, 33 (1912).

(7) Ch. Grundmann and G. Weisse, *Ber.*, **84**, 686 (1951).

(8) K. Hamann and W. Bauer (to Farbenfabriken Bayer), German Patent 825,547 (*Chem. Zentr.*, **93**, 6439 (1922); H. Welz and J. Weise (to Farbenfabriken Bayer), German Patent 837,691 (*Chem. Zentr.*, **93**, 5815 (1922).

intermediate quaternary salt, but its hydrolysis did not yield the desired aldehyde Vd.

The oxidation of 4,6-dimethoxy-2-hydroxymethyl-*s*-triazine (VIII) with manganese dioxide in the modification of Attenburrow, *et al.*,[9] also failed to produce the aldehyde Vd.

The 2-dibromomethyl-4,6-dimethoxy-*s*-triazine (IX) did not react with calcium carbonate (in water), hydroxylamine or potassium acetate, but was converted smoothly by methanolic sodium hydroxide into trimethyl cyanurate (X). The same reaction occurred with the 2-dichloromethyl-4,6-dimethoxy-*s*-triazine (XI). The proteolytic fission of halogenomethyl groups from *s*-triazine has been observed already on several occasions.[10] When IX and XI, however, were treated with sodium methoxide, no cleavage occurred and the expected 4,6-dimethoxy-*s*-triazine-6-aldehyde dimethylacetal (XII) was obtained. As previously experienced by Wystrach and Erickson[4] in a similar case, it was not possible to proceed from XII to the free aldehyde Vd or any other derivatives thereof. The acetal XII did not react with the hydrochlorides of hydroxylamine and semicarbazide in boiling methanol. Attempts to hydrolyze XII with diluted aqueous mineral acids resulted surprisingly in the formation of trimethyl cyanurate (X). Under more rigid conditions only cyanuric acid was formed.

Acknowledgment.—We are very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work.

Experimental[11]

4,6-Bis-thiomethyl-*s*-triazine-2-aldehyde Hydrazone (IIb).—An amount of 47.5 g. of 2-diazomethyl-4,6-dichloro-*s*-triazine (Ia) was stirred at 0° into a solution of 11.5 g. of sodium in 500 ml. of absolute ethanol and 100 g. of methanethiol. The reaction mixture was stirred for one day at room temperature. Then the precipitate was filtered off and extracted five times with hot ethanol. After standing for a while at −20° the hydrazone IIb (35 g.) crystallized from the extracts. A further 11.5 g. was obtained upon concentration of the mother liquor and cooling down, thus increasing the yield to 87.5%. The hydrazone IIb could be recrystallized from aqueous acetone, yielding fine yellow needles, m.p. 179–181°.

Anal. Calcd. for $C_6H_9N_5S_2$: C, 33.47; H, 4.21; N, 32.53; S, 29.79. Found: C, 33.43; H, 4.28; N, 32.45; S, 29.93.

Compound IIb also was obtained when a sample of 4,6-bis-thiomethyl-2-diazomethyl-*s*-triazine (Ib) was dissolved in a mixture of ethanol and methanethiol. After standing for two days the precipitated hydrazone was filtered off and recrystallized as described above. A mixed melting point did not show any depression.

4,6-Bis-thioethyl-*s*-triazine-2-aldehyde Hydrazone (IIc).—The amount of 4.75 g. of 2-diazomethyl-4,6-dichloro-*s*-triazine (Ia) was stirred with a solution of 1.15 g. of sodium metal in 100 ml. of ethanol, and 20 g. of ethanethiol for 7 hours at room temperature. The sodium chloride was removed by filtration and the filtrate concentrated. The resulting precipitate was filtered off with suction and dried on a clay plate, yielding 4.1 g. (67%) of IIc, m.p. 138–139° after recrystallization from ligroin.[12]

Anal. Calcd. for $C_8H_{13}N_5S_2$: C, 39.48; H, 5.38; N, 28.78. Found: C, 39.85; H, 5.40; N, 29.13.

The same hydrazone (IIc) was obtained when 2.4 g. of the 4,6-bis-thioethyl-2-diazomethyl-*s*-triazine (Ic) was dissolved in a mixture of 50 ml. of ethanol and 10 ml. of methanethiol. After standing for two days at room temperature the reaction mixture was concentrated. The resulting precipitate was filtered off and recrystallized from ligroin, yielding 1.6 g. (65%) of IIc, m.p. 138–139°.

4,6-Dimethoxy-*s*-triazine-2-aldehyde Hydrazone (IId).—The amount of 4.5 g. of 2-diazomethyl-4,6-dimethoxy-*s*-triazine (Id) was dissolved in 100 ml. of methanol at 0° and 25 g. of methanethiol was added. The reaction mixture was stirred at 0° for two hours and then allowed to warm up to room temperature. After standing for three days, yellow needles (2.25 g.) had separated, m.p. 210–212°. A further 1.0 g. of the hydrazone IId could be obtained from the mother liquor by concentrating and cooling down the concentrate to −20°, thus increasing the yield to 71%.

The same product IId was formed in a 78% yield when ethanethiol instead of methanethiol was used in the above described procedure.

When a slow stream of dry hydrogen sulfide was passed through a solution of 4.5 g. of 2-diazomethyl-4,6-dimethoxy-*s*-triazine (Id) in 100 ml. of methanol for six hours at room temperature, the hydrazone IId besides some sulfur precipitated from the solution after standing for one day. After recrystallization from ethanol IId melted at 212–213° (3.93 g., 85%). For final purification the hydrazone was sublimed at 0.5 mm. between 180 and 190°, yielding a slightly yellow powder.

Anal. Calcd. for $C_6H_9N_5O_2$: C, 39.34; H, 4.84; N, 38.24. Found: C, 39.10; H, 4.84; N, 38.46.

4,6-Dihydroxy-2-methoxymethyl-*s*-triazine (IV).—A solution of 2-diazomethyl-4,6-dichloro-*s*-triazine (Ia, 4.75 g.) in a mixture of 100 ml. of methanol and 10 g. of methanethiol was kept for four days at room temperature. Ether (1200 ml.) was added to the clear solution whereupon IV separated. It was recrystallized from acetic acid, m.p. 198–200°.

Anal. Calcd. for $C_5H_7N_3O_3$: C, 38.21; H, 4.49; N, 26.75. Found: C, 37.95; H, 4.45; N, 27.27.

4,6-Bis-thiomethyl-*s*-triazine-2-aldehydebenzylidene Hydrazone (IIIb).—The mixture of 4.3 g. (0.02 mole) of the hydrazone of the 4,6-bis-thiomethyl-*s*-triazine-2-aldehyde (IIb) and 6.7 g. (0.06 mole) of benzaldehyde in 50 ml. of absolute ethanol was refluxed for three hours. After standing at room temperature overnight, 4.6 g. of yellow needles had precipitated, m.p. 144–144.5°. The yield could be increased by concentrating the alcoholic mother liquor and cooling down the concentrate to −20°.

The azine IIIb was recrystallized from ligroin, yielding yellow, tufted, silky needles, m.p. 144–145°.

Anal. Calcd. for $C_{13}H_{13}N_5S_2$: N, 23.10. Found: N, 23.13, 22.99.

4,6-Bis-thioethyl-*s*-triazine-2-aldehydebenzylidene hydrazone (IIIc) was prepared analogously from the hydrazone IIc and benzaldehyde in ethanol; yield 51.5%, m.p. 74° (from ligroin).

Anal. Calcd. for $C_{15}H_{17}N_5S_2$: C, 54.36; H, 5.17; N, 21.13; S, 19.35. Found: C, 54.46; H, 5.16; N, 20.91; S, 19.39.

4,6-Dimethoxy-*s*-triazine-2-aldehydebenzylidene Hydrazone (IIId).—From 3.66 g. of the hydrazone IId, 2.5 g. of IIId was obtained in the same manner as described above. The azine IIId was recrystallized from ligroin, yielding yellow plates, m.p. 151–152°.

Anal. Calcd. for $C_{13}H_{13}N_5O_2$: C, 57.86; H, 4.83; N, 25.82. Found: C, 57.80; H, 4.81; N, 26.23.

4,6-Bis-thiomethyl-*s*-triazine-2-aldehyde (Vb).—The mixture of 13 g. of the hydrazone of the 4,6-bis-thiomethyl-*s*-triazine-2-aldehyde (IIb) and 24 g. of 2,4-dinitrobenzaldehyde in 200 ml. of ethyl alcohol and 10 ml. of water was refluxed for 15 hours. After cooling and filtering from the dinitrobenzalazine the solvents were removed *in vacuo*, yield-

(9) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(10) A. Weddige, *J. prakt. Chem.*, [2] **33**, 8 (1886); N. Tscherven-Iwanoff, *ibid.*, [2] **46**, 142 (1892); E. Ghigi, *Gazz. chim. ital.*, **71**, 641 (1941); Ch. Grundmann and G. Weisse, *Ber.*, **84**, 684 (1951); H. Schroeder and Ch. Grundmann, THIS JOURNAL, **78**, 2447 (1956).

(11) Melting points were determined with the Fisher-Johns apparatus. Microanalyses were by the Galbraith Laboratories, Knoxville, Tenn., and by Spang Microanalytical Laboratories, Ann Arbor, Mich.

(12) If not indicated otherwise, here and in the following, a fraction, boiling from 90–97°, was used.

ing a dark oily residue which was extracted with ligroin. The extracts were kept at −25° for a few days, whereupon white crystalline spheroids (5.05 g., 33.4%) precipitated which were identified as the **hemi-ethyl acetal of the 4,6-bis-thiomethyl-*s*-triazine-2-aldehyde.**

When the hemi-acetal was sublimed twice between 70 and 120° at 0.5 mm., 3.4 g. of the free aldehyde Vb was obtained in the form of yellowish crystals, m.p. 102–102.5°.

Anal. Calcd. for $C_5H_7N_3OS_2$: C, 35.81; H, 3.50; N, 20.88; S, 31.86. Found: C, 35.86; H, 3.42; N, 21.04; S, 31.91.

The free aldehyde could be reconverted into the hemi-ethyl acetal by dissolving it in a small amount of ethyl alcohol. Upon cooling down to −25°, felted, silver-white needles precipitated, m.p. 57–58°.

Anal. Calcd. for $C_8H_{13}N_3O_2S_2$: C, 38.85; H, 5.29; N, 17.00; S, 25.93. Found: C, 38.88; H, 5.31; N, 17.15; S, 25.97.

The free aldehyde formed a sesqui-hydrate, $C_6H_7N_3OS_2 \cdot 1.5H_2O$, when dissolved in a small amount of warm water. Upon cooling, the sesqui-hydrate precipitated in form of long, felted, white needles, m.p. 88–89°.

Anal. Calcd. for $C_6H_7N_3OS_2 \cdot 1.5H_2O$: C, 31.56; H, 4.41; N, 18.41; S, 28.09. Found: C, 31.52; H, 4.44; N, 18.29; S, 28.15.

The thio-semicarbazone of the 4,6-bis-thiomethyl-*s*-triazine-2-aldehyde was obtained in a 98% yield when equivalent amounts of Vb and thiosemicarbazide were refluxed in aqueous ethanol for three hours; yellow needles, m.p. 256° dec.

Anal. Calcd. for $C_7H_{10}N_6S_3$: C, 30.64; H, 3.67; N, 30.63; S, 35.06. Found: C, 30.70; H, 3.61; N, 30.61; S, 35.12.

4,6-Dimethoxy-*s*-triazine-2-aldehyde (Vd).—The mixture of 13.74 g. of the hydrazone of the 4,6-dimethoxy-*s*-triazine-2-aldehyde (IId) and 29.4 g. of 2,4-dinitrobenzaldehyde in 140 ml. of ethanol and 6 ml. of water was refluxed for 8 hours. After cooling, the dinitrobenzalazine was filtered off. The solvents were removed *in vacuo* from the filtrate, yielding an oily residue which was extracted with boiling ligroin. The extracts were kept at −25° for two days, whereupon white crystalline spheroids besides a yellowish oil was obtained.

On vacuum distillation this oil passed over at 111–114° (1 mm.). The crude aldehyde Vd (2.4 g., 19%) soon solidified and was further purified by recrystallization from ligroin (b.p. 30–38°) and by vacuum sublimation (60–75° (0.5 mm.) Hg); colorless needles, m.p. 74–75°, were so obtained.

Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.60; H, 4.17; N, 24.84. Found: C, 42.64; H, 4.03; N, 24.89.

The above-mentioned white crystalline spheroids (0.5 g.) which precipitated from the ligroin extracts turned out to be the **hemi-ethyl acetal of Vd**, m.p. 51–52°.

Anal. Calcd. for $C_8H_{13}N_3O_4$: C, 44.63; H, 6.04; N, 19.54. Found: C, 44.70; H, 5.94; N, 19.56.

When this hemi-acetal was sublimed between 75 and 125° at 0.2 mm. the free aldehyde Vd was obtained, thus increasing the over-all yield to 22.2%.

The free aldehyde is hygroscopic. With water it formed a stable hydrate $C_6H_7N_3O_3 \cdot H_2O$. This hydrate was best obtained by dissolving the aldehyde in a small amount of water and extracting this solution with ether. The ether removed mainly traces of impurities and only a small amount of the hydrate. The aqueous solution was then slowly evaporated at room temperature in a desiccator over calcium chloride. The hydrate remained in form of leaflets with a mother-of-pearl luster, m.p. 83–85°.

Anal. Calcd. for $C_6H_9N_3O_4$: C, 38.50; H, 4.84; N, 22.46. Found: C, 38.55; H, 4.75; N, 22.45.

The thiosemicarbazone of the 4,6-dimethoxy-*s*-triazine-2-aldehyde was obtained in a 100% yield, when equivalent amounts of the aldehyde Vd and thio-semicarbazide were refluxed for five hours in 50% aqueous alcohol; slight yellowish fine needles, m.p. 222–223° dec.

Anal. Calcd. for $C_7H_{10}N_6O_2S$: C, 34.70; H, 4.16; N, 34.70; S, 13.23. Found: C, 34.80; H, 4.10; N, 34.97; S, 13.11.

Polymerization of the Aldehydes Vb and Vd.—Finely powdered samples (1.0 g.) of 4,6-bis-thiomethyl-*s*-triazine-2-aldehyde (Vb) and 4,6-dimethoxy-*s*-triazine-2-aldehyde (Vd) were exposed on a shallow dish to the air for 75 days. After this period the main part of the material still consisted of the unchanged monomers, Vb resp. Vd, which could be removed by extraction with cold ethanol. The polymers remained insoluble as colorless microcrystalline powders; 0.42 g. polymer from Vb, m.p. 106–112°, and 0.07 g. of polymer from Vd, m.p. 124–135°.

Anal. Calcd. for $(C_6H_7N_3OS_2)_x$: C, 35.81; H, 3.50; N, 20.88; S, 31.86. Found: C, 35.21; H, 3.77; N, 20.77; S, 31.21. Calcd. for $(C_6H_7N_3O_3)_x$: C, 42.60; H, 4.17; N, 24.84. Found: C, 42.55; H, 4.29; N, 24.88.

Both polymers were insoluble at room temperature in all common organic solvents. Boiling with a suitable solvent, *e.g.*, toluene, for several minutes, slowly effected solution of the polymers with simultaneous depolymerization. The monomers, Vb resp. Vd, crystallized from these solutions. These properties of the polymers inhibited any molecular weight determination by cryoscopic or ebullioscopic techniques. The Rast method yielded, as could be expected, the values for the monomers.

Reaction of 2-Chloromethyl-4,6-dimethoxy-*s*-triazine (VII) with Nitrocyclohexane.—The triazine VII (0.06 mole) and an equivalent amount of sodium nitrocyclohexane in methanol (250 ml.) were stirred at room temperature for 20 hours. On working up the reaction mixture, besides a small amount of cyclohexanone oxime, a considerable part of the starting materials was recovered unchanged. The reaction product (about 30% of the charged VII) could be separated after acidifying by means of ether into two unidentified compounds A and B; A was nearly insoluble in ether and ethanol, but could be recrystallized from water, forming fine needles, m.p. 217–219°.

Anal. Calcd. for $C_{12}H_{11}N_5O_4$: C, 45.25; H, 4.15; N, 26.40. Found: C, 44.99, 44.98; H, 4.09, 4.12; N, 26.39, 26.51.

Compound B was very soluble in ether, soluble in methanol, and nearly insoluble in water, but formed a water-soluble sodium salt with sodium ethoxide in ethanol. Recrystallized from aqueous methanol, the obtained needles melted at 122–123°.

Anal. Calcd. for $C_5H_6N_4O_4$: C, 32.27; H, 3.23; N, 30.10. Found: C, 32.46; H, 2.87; N, 30.37.

Obviously, both compounds are triazine derivatives, but without any recognizable relation to the desired aldehyde Vd.

Trimethylcyanurate from 2-Dibromomethyl- resp. 2-Dichloromethyl-4,6-dimethoxy-*s*-triazine (IX resp. XI).—Pure 2-dibromomethyl-4,6-dimethoxy-*s*-triazine (4.7 g.) was refluxed for 6 hours with the solution of 1.2 g. of sodium hydroxide in 40 ml. of methanol. The alcohol was then removed *in vacuo* from the dark neutral solution. Water was added to the residue and the mixture extracted three times with ether. The ether was removed from the combined extracts, yielding 1.03 g. of slightly yellowish needles, which were recrystallized from ligroin. A mixed melting point with trimethyl cyanurate (X) was without depression.

The same experiment with the dichloromethyl-4,6-dimethoxy-*s*-triazine (XI) instead of IX resulted also in the formation of 0.81 g. of trimethyl cyanurate.

Anal. Calcd. for $C_6H_9N_3O_3$: C, 42.10; H, 5.27; N, 24.56. Found: C, 42.22; H, 5.25; N, 24.53.

4,6-Dimethoxy-2-dimethoxymethyl-*s*-triazine (XII).—The amount of 9.4 g. (0.03 mole) of 2-dibromomethyl-4,6-dimethoxy-*s*-triazine (IX) was dissolved in the ice-cold solution of 1.38 g. (0.06 moles) of sodium metal in 250 ml. of methanol upon stirring. The reaction mixture was refluxed for seven hours, the methanol distilled off and the remaining solid residue extracted with ether. The ethereal extract was evaporated. The resulting oil crystallized upon standing at 0° for one day. The crude XII (5.25 g., 81.4%) was recrystallized from ligroin, yielding white needles, m.p. 40–41°.

Anal. Calcd. for $C_8H_{13}N_3O_4$: C, 44.63; H, 6.04; N, 19.54. Found: C, 44.47; H, 6.04; N, 19.65.

Compound XII also was obtained analogously from 2-dichloromethyl-4,6-dimethoxy-*s*-triazine (XI), but even after refluxing the reaction mixture for 16 hours the yield was only 10.4%.

Acid Hydrolysis of XII.—An amount of 5.25 g. of XII was dissolved in a mixture of 30 ml. of 1 *N* sulfuric acid and 30 ml. of acetone. The reaction mixture was kept at 25° for

one hour and then heated up to 45° for 10 minutes. When the acetone was removed *in vacuo* at room temperature, fine white needles precipitated (1.0 g., 36%). After recrystallization from ligroin the needles had a melting point of 132–133°. A mixed melting point with an authentic sample of trimethyl cyanurate (X) was without depression.

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Protein Binding of Model Quinone Imides. I. The Synthesis of Some Fluorenoquinone Imides[1]

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The *o*-quinone monoimides, 1,2-fluorenoquinone-2-acetimide and 1,2-fluorenoquinone-2-benzimide, were prepared by lead tetraacetate oxidation of N-(1-hydroxy-2-fluorenyl)-acetamide and of N-(1-hydroxy-2-fluorenyl)-benzamide, respectively. These compounds were desired for a study of their interaction with proteins. The preparation of 4,4′-diphenoquinone-4-*p*-tolylsulfonimide and of 2,7-fluorenoquinone-2-*p*-tolylsulfonimide by lead tetraacetate oxidation of the respective amidophenols was attempted in order to explore the possibility of synthesizing quinone monoimides with conjugation extending through two adjacent aromatic rings. The former compound was obtained in pure form, while the latter was unstable and polymerized extensively upon attempted purification. In contrast, the quinone diimide, 2,7-fluorenoquinone-dibenzenesulfonimide, was prepared readily by lead tetraacetate oxidation of 2,7-bis-(benzenesulfonamido)-fluorene. The oxidation products were characterized by infrared and electronic spectra, by reduction to starting material and/or addition of hydrogen chloride.

The binding of a variety of carcinogenic compounds or of metabolites thereof to tissue proteins is currently considered a causative factor in the induction of neoplasms by chemical agents.[2,3] In the majority of instances the identity of these reactive metabolites remains to be determined. In the case of the carcinogen N-(2-fluorenyl)-acetamide the suggestion has been made that the reactive species which interact with cellular protein are quinone imides or quinone imines.[4] These compounds were thought to arise from the intracellular oxidation of hydroxylated intermediates. The latter compounds have been recognized as metabolites of N-(2-fluorenyl)-acetamide.[5] Recent work has provided experimental evidence that enzymatic oxidation of 2-amino-1-fluorenol yielded in fact a product which required the intermediate formation of the corresponding *o*-quinone imine.[6] For an unequivocal proof of the interaction of *o*-fluorenoquinone imines with proteins as well as for a systematic investigation of the mechanism of this reaction it became necessary to synthesize these compounds in quantities sufficient to carry out these studies.

Preliminary experiments showed that 2-amino-1-fluorenol was oxidized by lead tetraacetate, as indicated by appearance of a red color with maximum absorption at 450 mμ; however, attempts to isolate the oxidation product were unsuccessful. Isolation of the *o*-quinone imides derived from N-(1-hydroxy-2-fluorenyl)-benzamide or N-(1-hydroxy-2-fluorenyl)-acetamide appeared more promising in view of the work of Adams and Stewart.[7] These investigators described the preparation of *o*-quinone imides by oxidation of several *o*-amidophenols with lead tetraacetate and showed that successful oxidation required stabilization of the quinonoid system by substitution *para* to the amido group. The aforementioned amidofluorenols may be looked upon as *o*-amidophenols in which this position is occupied by the phenyl group and which therefore satisfy the above requirement. As expected, the respective *o*-quinone imides were obtained readily as bright-red crystalline solids which proved to be indefinitely stable and which interacted rapidly and irreversibly with crystalline bovine serum albumin.[8] The compounds were quite soluble in a number of organic solvents such as chloroform or dioxane to give bright red solutions; however, their stability in solution at room temperature was limited, as evidenced by brownish discoloration after short periods of standing. Since Adams and Stewart[7] were unable to isolate the oxidation product of 6-acetamido-*m*-cresol while 1,2-fluorenoquinone-2-acetimide proved to be a stable compound, it would appear that the phenyl group lends greater stability to the *o*-quinonoid system than the methyl group. The stability of *o*-fluorenoquinone imides in which the quinonoid structure was confined to one aromatic ring prompted the question whether equally stable oxidation products could be prepared when the conjugation was extended to involve two adjacent phenyl rings as in diphenoquinone dibenzenesulfonimide.[9] Accordingly, the oxidation of 2,7-bis-(benzenesulfonamido)-fluorene and of N-(7-hydroxy-2-fluorenyl)-*p*-tolylsulfonamide was attempted. In the case of the former compound, a stable diimide was obtained which exhibited physical properties closely resembling those of diphenoquinone dibenzenesulfonimide.[9] Oxidation of the latter compound yielded an unstable quinone mono-

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