s-Triazines. III.[1a] Novel Mode of Formation of Some 1,2-Dihydro-s-triazines

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A by-product from reactions of trimethyl cyanurate or of 2-ethyl-4,6-dimethoxy-s-triazine with ethylmagnesium chloride was assigned structure I ($R_1 = R_2 = C_2H_5$).[1a]

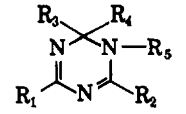
I

This Note describes the preparation of dihydro-s-triazines I by an entirely different route. Schaefer[2] prepared unsymmetrically substituted s-triazines by reaction of amidine salts with imidates. Reinvestigation of the condensation of O-methylisourea salts with isopropyl propionimidate showed that this particular reaction proceeds best in the presence of small amounts of alcohols.[3]

When acetone was used as reaction medium, practically no triazines were formed, and the only product isolated was the dihydro-s-triazine I ($R_1 = R_2 = CH_3$). This compound showed infrared absorption very similar to that of the previously isolated I ($R_1 = R_2 = C_2H_5$).[1a]

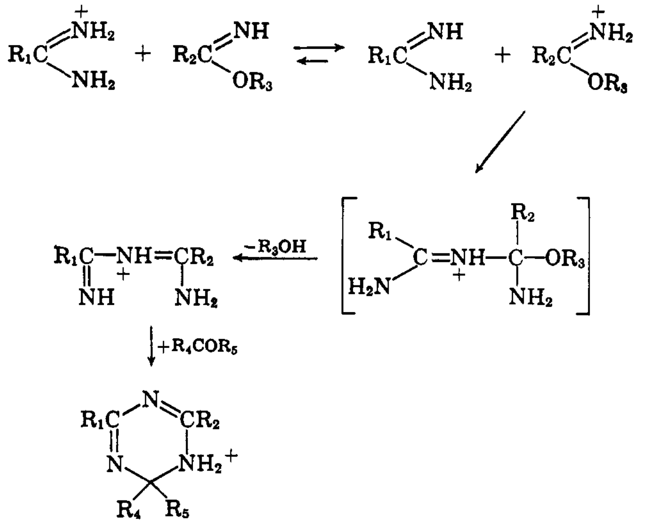
Indeed, condensation of O-methylisourea tosylate with isopropyl propionimidate in the presence of excess pentan-3-one gave I ($R_1 = R_2 = C_2H_5$) in a very low yield. Thus its structure is established by two independent routes of formation.

The compound I constitutes a new type of 1,2-dihydro-s-triazine. Two groups of dihydro-s-triazines have hitherto received attention. The ones prepared by the action of bases on aromatic nitriles are all related to triphenyl-s-triazine (II, $R_1 = R_2 = R_3 = Ph$; $R_4 =$ alkyl; $R_5 =$ H or alkyl).[4] The others, many of which are endowed of various biological activities (and were the subject of extensive study by Carrington and coworkers and by Modest and his collaborators[5a]) are diaminodihydro-s-triazines II ($R_1 = NH_2, NHR$; $R_2 = NHAr, NRAr$; $R_3 =$ alkyl; $R_4 =$ H, alkyl, or aryl; $R_5 =$ H) and II ($R_1, R_2 = NH_2, NHR,$ or NR_2; $R_3 =$ alkyl; $R_4 =$ H, alkyl, or aryl; $R_5 =$ aryl or alkyl, and recently extended to alkoxy and aralkoxy[5b]).



II

Formation of dihydrotriazines can be visualized as involving the same intermediates as those postulated by Schaefer for the syntheses of s-triazines by trimerization of imidates and in the reaction of amidine salts with imidates.[2,6]



The scope of the reaction is, however, very limited. Moderate yields of dihydro-s-triazines I were obtained only with aliphatic methyl ketones. Acetophenone, benzaldehyde, and propionaldehyde gave rise to oily products, other than I, which have not as yet been identified. When O-methylisourea was replaced by other amidines (acetamidine, guanidine, 1,1-dimethylguanidine, or S-methylisothiourea), again no dihydro-s-triazines were formed.

Experimental[7]

6-Ethyl-4-methoxy-2,2-dimethyl-1,2-dihydro-s-triazine (I, $R_1 = R_2 = CH_3$).—A mixture of 1.38 g. of isopropyl propionimidate (prepared following the conditions used for ethyl propionimidate[8]; b.p. 116°, n^{30}_{D} 1.4061), 2.94 g. of O-methylisourea p-toluenesulfonate,[9] and 20 ml. of acetone was stirred and heated under reflux for 20 hr. by which time complete dissolution occurred. The solution was evaporated to dryness, the residue was dissolved in methylene chloride, and the insoluble O-methylisourea tosylate (0.29 g.) was filtered. The mother liquor was treated with a po-

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(1) (a) Part II: H. Bader, E. R. Ruckel, F. X. Markley, S. G. Santangelo, and P. Schikedantz, *J. Org. Chem.*, **30**, 702 (1965). (b) To whom correspondence should be addressed at Aldrich Chemical Co., Milwaukee, Wis.

(2) F. C. Schaefer, *J. Org. Chem.*, **25**, 3608 (1962).

(3) In this case 2-propanol is usually present with the imidate base. However, this finding is not a general one, *e.g.*, S-methylisothiourea reacts readily with isopropyl propionimidate even in the absence of alcohols (D. S. Allen, private communication).

(4) For review see (a) E. M. Smolin and L. Rapoport, "s-Triazines and Derivatives," Interscience Publishers, Inc., New York, N. Y., 1959, p. 179 ff.; and (b) E. J. Modest, "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 695 ff.

(5) (a) For detailed accounts see ref. 4a, p. 258 ff., and ref. 4b, pp. 697–701 and 717–719; (b) P. Mamalis, J. Green, D. J. Outred, and M. Rix, *J. Chem. Soc.*, 3915 (1962).

(6) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2784 (1961).

(7) All melting points are corrected. The infrared spectra were determined with a Perkin-Elmer Infracord spectrophotometer as a Nujol mineral oil mull. Microanalyses were carried out in these laboratories by Mr. John J. Kobliska and his staff.

(8) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

(9) J. W. Janus, *J. Chem. Soc.*, 3551 (1955).

tassium carbonate solution which was separated and extracted with methylene chloride. The combined organic extracts were dried and the solvent was removed. The residue crystallized from ether in long colorless needles: 0.80 g. (39.4% yield); m.p. 126–126.5°; and infrared absorption, 3160 (NH stretching) and 1635 cm.$^{-1}$ (C=N stretching in nonresonating systems).

Anal. Calcd. for $C_8H_{15}N_3O$: C, 56.78; H, 8.93; N, 24.84. Found: C, 56.98; H, 9.24; N, 24.63.

2,2,6-Triethyl-4-methoxy-1,2-dihydro-*s*-triazine (I, $R_1 = R_2 = C_2H_5$).—A mixture of 1.38 g. of isopropyl propionimidate, 2.94 g. of O-methylisourea *p*-toluenesulfonate, 5 ml. of diethyl ketone, and 15 ml. of benzene was heated under reflux and stirred for 8 hr. Work-up in the manner described above yielded 1.93 g. of recovered O-methylisourea salt and, after crystallization from ether, 0.065 g. (2.7%) of I ($R_1 = R_2 = C_2H_5$) in long colorless prisms, m.p. 142–143.5°. This was shown through comparison of infrared spectra and mixture melting point to be identical with a sample, m.p. 143–145°, obtained by a different route.[1a]

2,6-Diethyl-4-methoxy-2-methyl-1,2-dihydro-*s*-triazine (I, $R_1 = CH_3$; $R_2 = C_2H_5$).—A mixture of 1.38 g. of isopropyl propionimidate and 2.94 g. of O-methylisourea *p*-toluenesulfonate in 5 ml. of methyl ethyl ketone and 10 ml. of 2-propanol became homogeneous at reflux. After heating under reflux for 2.5 hr. and work-up in the manner described above, 1.24 g. of O-methylisourea salt was recovered. Evaporation of the methylene chloride extract gave 1.27 g. of crude product, which on crystallization from pentane afforded 0.74 g. (33.7%) of I ($R_1 = CH_3$; $R_2 = C_2H_5$) in needles and hexagonal prisms: m.p. 121–122°; infrared absorption, 3120 and 1635 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{17}N_3O$: C, 58.98; H, 9.35; N, 22.93. Found: C, 59.12; H, 9.14; N, 22.40.

The Preparation of Hydrazidines and *as*-Triazines Related to Substituted 2-Cyanopyridines[1]

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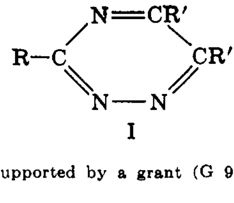
The preparation of hydrazidines of the formula RC(=NH)NHNH$_2$ has previously been accomplished by the action of hydrazine on the corresponding thioamide[2] or imido ether.[3,4] Less commonly (as in the case of cyanothiazole[4]) they have been prepared by direct action of hydrazine on the nitrile.

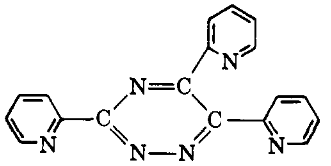
In this laboratory the latter procedure has been applied successfully to 2-cyanopyridine and several of its substitution products as well as 2-cyanoquinoline, 2-cyanopyrimidine, and 2-cyano-1,10-phenanthroline. (The preparation of the last-mentioned compound as well as that of 5-cyano-1,10-phenanthroline is described in the Experimental section.) The resulting hydrazidines, which contain the "ferroin" group, =N—C=C—N=, give a deep red color with Fe(II).

It has further been found that the above hydrazidines with the exception of that from 2-cyanopyrimidine condense readily with benzil and pyridil to form 3,5,6-trisubstituted *as*-triazines of formula I.



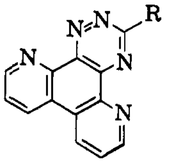
I

Thus, II, resulting from the action of the hydrazidine from 2-cyanopyridine and pyridil, containing three ferroin groups, gives a very sensitive test for Fe(II).



II

By condensing the hydrazidines with 4,7-phenanthroline-5,6-dione,[5] a number of 3-substituted *as*-triazino[5,6-*f*][4,7]phenanthrolines (III) were prepared.

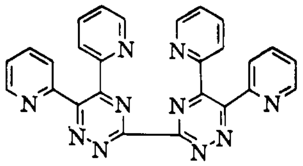


III

Most of these formed with Fe(II) very deep blue complexes.

Previously 5,6-diphenyl-3(3- and 4-pyridyl)-*as*-triazines have been prepared by the action of the corresponding acylhydrazine with benzil and ammonia.[6,7]

We have also prepared tetrakis(2-pyridyl)-3,3′-bi(*as*-triazine) (IV) by the action of oxamide dihydrazone, H$_2$N-N=C(NH$_2$)(NH$_2$)C=N—NH$_2$, on pyridyl. The corresponding tetraphenyl derivative has previously been reported.[8]



IV

For the preparation of oxamide dihydrazone the action of 95% hydrazine in ethanol on dithiooxamide was found simpler than the previous method (cyanogen and hydrazine[8]).

Experimental

Preparation of Hydrazidines.—A mixture of 0.05 mole of nitrile, 9 ml. of ethanol, and 15 ml. of 95% hydrazine was stirred at room temperature for 2 hr. It was then diluted with an equal volume of water, extracted with ether, and dried over anhydrous sodium sulfate. After removal of ether, the residue was crystallized from the solvent indicated in Table I. The hydrazidines from 2-cyano-4-phenylpyridine, 2-cyanoquinoline, and 2-cyano-1-10-phenanthroline precipitated out on addition of water, and no ether extraction was necessary. In the case of the last-mentioned compound, the proportions of nitrile, 95% hydrazine, and ethanol were 0.008 mole, 5 ml., and 5 ml., respectively. The hydrazine from 2-cyanothiazole was prepared according to the directions of Libman and Slack.[4]

Preparation of 3-Substituted 5,6-Diphenyl-*as*-triazines.—Mixtures of 0.02 *M* quantities of hydrazidine and benzil in 25 ml.

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[2] W. Van der Burg, *Rec. trav. chim.*, **74**, 257 (1955).

[3] A. Pinner, *Ber.*, **27**, 985 (1894); *Ann.*, **297**, 221 (1897).

[4] D. Libman and R. Slack, *J. Chem. Soc.*, 2253 (1956).

[5] J. Druey and P. Schmidt, *Helv. Chim. Acta*, **33**, 1085 (1950).

[6] P. Laakso, R. Robinson, and H. Vandrewala, *Tetrahedron*, **1**, 103 (1957).

[7] C. Atkinson and H. Cossey, *J. Chem. Soc.*, 1805 (1962).

[8] G. Dedichen, *Avhandl. Norske Videnskaps-Akad. Oslo*, **5**, 42 (1936); *Chem. Abstr.*, **31**, 4985^3 (1937).